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[redacted]

VIA CM/ECF & HAND DELIVERY
The Honorable Colm F. Connolly
J. Caleb Boggs Federal Building
844 N. King Street
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PUBLIC VERSION FILED:
MARCH 15, 2019

March 8, 2019

Re: ***Genentech, Inc. v. Amgen Inc.*, C.A. No. 17-1407-CFC (D. Del.) (consolidated)**

Dear Judge Connolly:

Genentech wishes to raise four issues at the March 12, 2019 discovery conference.

1. Protective Order and New Complaint. This past summer Amgen [redacted] After Amgen provided the [redacted] to Genentech in discovery, Genentech on October 10, 2018 advised the Court that the [redacted] would trigger a new lawsuit once the parties completed the "patent dance" procedures set forth in 42 U.S.C.§ 262(*l*).[1]

Shortly thereafter, and pursuant to 42 U.S.C. § 262(*l*)(3)(a), Genentech sent Amgen a list of patents infringed by the [redacted] Genentech listed some of the same patents asserted in the pending cases but also included two others [redacted] Amgen's response under § 262(*l*)(3)(B) was due December 18. Two days before that Amgen announced it was forgoing the "patent dance" and took the position that Local Rule 26.2/the Protective Order prohibited not only any formal BPCIA exchanges but also any new lawsuit by Plaintiffs based on the [redacted]

Amgen's position is meritless. Protective orders may be modified for any good reason following balancing of the parties' interests. *Pansy v. Borough of Stroudsburg*, 23 F.3d 772, 790 (3d Cir. 1994). "In this vein, a factor to consider is whether the information is being sought for a legitimate purpose or for an improper purpose." *Id.* at 787. Plaintiffs' purpose in modifying the Protective Order—vindicating their rights upon the discovery of additional claims—is obviously

[1] D.I. 186 at 122:11-17 ("This summer it [Amgen] applied for [redacted] to make the stuff through a, what appears to be a [redacted] . . . So we've gotten that application. We are reviewing it."); *see also* Tr. 122:18-22 ("We already have two cases . . . and there's going to be a third.").

proper. Amgen's purpose in opposing—shielding its conduct from legal scrutiny—is not. After all, courts enter protective orders to protect the secrecy of the parties' confidential information. Fed. R. Civ. P. 26(c)(1)(G). They are not a device to prevent a party from asserting its rights, under seal, upon discovery of additional claims. *See, e.g., CBS Interactive, Inc. v. Etilize, Inc.*, 257 F.R.D. 195, 205-06 (N.D. Cal. 2009) (modifying protective order to permit filing second lawsuit); *Verizon Ca. Inc. v. Ronald A. Katz Tech. Lic'g L.P.*, 214 F.R.D. 583, 586 (C.D. Cal. 2003) (modifying to permit use in second lawsuit); 8A Fed. Prac. & Proc. Civ. § 2044.1 (3d ed.) (discussing "long line of cases recognizing the propriety of access to the fruits of one litigation to facilitate the preparation of other cases"). Nevertheless, to avoid a dispute Genentech on January 28, 2019 sent Amgen both a draft complaint addressing the infringement disclosed in the [redacted] and a proposal to modify the Protective Order to permit "litigation initiated by the filing of the Complaint provided by Genentech to Amgen on January 28, 2019." Ex. 2. After asking for additional time to consider the request, Amgen on February 21 refused to consent.

Amgen is not required to participate in the "patent dance," *Sandoz, Inc. v. Amgen Inc.*, 137 S. Ct. 1664, 1675 (2017), but it cannot block Plaintiffs from seeking relief under the Patent Act for the infringement [redacted] The Court should enter the requested modification to the Protective Order to allow this case to proceed.

2. "Ex-US" Documents and Redactions. Genentech has requested documents relating to Amgen's plans to sell Mvasi overseas, including its filings with and studies done for foreign regulatory agencies (RFP Nos. 111-113, 123). Amgen has refused to produce such documents and redacted from more than 1,600 documents what it labels "Ex-US" information, including [redacted] These documents should be produced, unredacted, for at least two reasons.

First, Amgen [redacted] Ex. 3 at 13. Such manufacturing is infringing, and information about Amgen's foreign plans is relevant to assessing damages. [redacted] *R.R. Dynamics, Inc. v. A. Stucki Co.*, 727 F.2d 1506, 1519 (Fed. Cir. 1984).

Second, Amgen is engaged in [redacted] Activities not required for U.S. approval are not protected by the Patent Act's "safe harbor," 35 U.S.C. § 271(e)(1). *See, e.g., NeoRx Corp. v. Immunomedics, Inc.*, 877 F. Supp. 202, 208 (D.N.J. 1994); *Ventrassist Pty Ltd. v. Heartware, Inc.*, 377 F. Supp. 2d 1278, 1287 n.10 (S.D. Fla. 2005). Documents that disclose actual infringement are unquestionably relevant.

3. Manufacturing Process Redactions & Documents. Various aspects of Amgen's manufacturing process for Mvasi are [redacted] Amgen's Rule 30(b)(6) witness testified: "[redacted] Request No. 128 accordingly seeks "[r]epresentative copies of

functional specifications, process validation reports, and/or batch records showing the processes by which Amgen's other biologic products are manufactured." By seeking only "representative copies," the request is proportional.

Amgen has refused to provide the requested documents, and it has redacted from documents it has produced information about the manufacturing processes [redacted] But Genentech needs these documents to understand how [redacted] including Amgen's reasons for choosing various manufacturing parameters (relevant to willfulness), the functions those parameters play in the process (relevant to validity and infringement), and the effect of modifying those parameters (relevant to damages, validity, and infringement). For example, one of the asserted patents claims a process involving insulin. [redacted] *See* Ex. 7 at 228:10-229:3, 235:16-236:20. Genentech contends that this [redacted] protein is equivalent to insulin, and it therefore needs (and is entitled to) discovery into Amgen's decision to use this particular input in its manufacturing process. *See, e.g.*, *Intendis GmbH v. Glenmark Pharms. Inc., USA*, 822 F.3d 1355, 1360-63 (Fed. Cir. 2016) (relying upon, *inter alia*, the infringer's stated reasons for using the equivalent). Genentech asks the Court to order production of the "representative copies" sought by Request No. 128 and the removal of redactions from documents Amgen has already produced.

4. Documents Inconsistent with Amgen's Justification for Stockpiling Mvasi. Amgen developed and uses a proprietary computer form— [redacted] Amgen now disparages its [redacted] tool as unreliable and refuses to produce documents relating to its development or use in other instances (RFP Nos. 129-131). This discovery is probative to rebut Amgen's attack on the reliability of its own operating procedures and to establish Amgen's intent when conducting its manufacturing, both of which bear on whether Amgen's pre-launch manufacturing is entirely immune from infringement under the regulatory "safe harbor," 35 U.S.C. § 271(e)(1). *See Amgen Inc. v. Hospira*, Inc. 336 F. Supp. 3d 333, 354-55 (D. Del. 2018) (evidence of commercial intent is relevant to whether pre-approval manufacturing is protected by safe harbor). The Court should order that it be produced.

EXHIBIT 1

THIS DOCUMENT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 2

THIS DOCUMENT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 3

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 November 2017
EMA/798844/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

MVASI

International non-proprietary name: bevacizumab

Procedure No. EMEA/H/C/004728/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ABP	Amgen Biosimilar Protein
ADA	anti-drug antibody
ADCC	antibody dependent cell-mediated cytotoxicity
ALK	anaplastic lymphoma receptor tyrosine kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATO	Amgen Thousand Oaks
AUC	area under the concentration-time curve
AWA	Amgen Washington
BMI	body mass index
CCI	container closure integrity
CD	circular dichroism
CDC	complement dependent cytotoxicity
CDISC	Clinical Data Interchange Standards Consortium
CDR	complementarity-determining region
CEX	cation exchange
CFR	Code of Federal Regulations (US)
cGMP	current good manufacturing practices
CHO	chinese hamster ovary
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CNS	central nervous system
CR	complete response
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trials Management System
CV	coefficient of variation
DEHP	diethylhexyl phthalate
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DNTA	5,5'-dithiobis-(2-nitrobenzoic acid)
DOR	duration of response
DP	drug product
DS	drug substance
DSC	differential scanning calorimetry
ECG	electrocardiogram
ECL	electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor

ELISA	enzyme-linked immunosorbent assay
EOI	event of interest
ESI-TOF-MS	electrospray ionization time-of-flight mass spectrometry
EU	endotoxin units
Fc	fragment crystallizable
FcR	fragment crystallizable receptor
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration (US)
FTIR	fourier-transformed infrared spectroscopy
GCP	good clinical practice
GFR	glomerular filtration rate
GI	gastrointestinal
HC	heavy chain
HCP	host cell protein
HIAC	high accuracy light obscuration particle counting
HIC	hydrophobic interaction chromatography
HPLC	high-performance liquid chromatography
HUVEC	human umbilical vein endothelial cells
HWP	high molecular weight
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IP	investigational product
IPC	in-process control
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IXRS	interactive voice and web response system
KM	Kaplan-Meier
LC	light chain
LC-MS/MS	liquid chromatography coupled to tandem mass spectrometry
LLN	lower limit of normal
LMWH	low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
N/A	not applicable
NCI	National Cancer Institute (US)
NE	not evaluable
NF	National Formulary
nrCE	non-reduced capillary electrophoresis
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
Ph Eur	European Pharmacopoeia

PIN	Personal Identification Number
PK	pharmacokinetic
PNGase	peptide-N4-(N-acetyl-beta-glucosaminyl)
PP	per protocol
PQR	product quality attribute
PR	partial response
PVC	polyvinyl chloride
p-y	patient-years
Q1	25th percentile
Q3	75th percentile
Q3W	every 3 weeks
rCE	reduced capillary electrophoresis
RD	risk difference
RECIST	Response Evaluation Criteria in Solid Tumors
RP-HPLC	reverse-phase high performance liquid chromatography
RPLS	reversible posterior leukoencephalopathy syndrome
RR	risk ratio
RTK	receptor tyrosine kinase
RTRT	real time release testing
SA	scientific advice
SAP	statistical analysis plan
SD	standard deviation/stable disease
SDS	sodium dodecyl sulfate
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Queries
SOC	system organ class
SOP	standard operating procedures
SPR	surface plasmon resonance
STD	standard deviation
TEAE	treatment-emergent adverse events
TSB	trypticase soy broth
TSE	transmissible spongiform encephalopathy
UF/DF	ultrafiltration/diafiltration
ULN	upper limit of normal
USP	United States Pharmacopeia
USPI	US Prescriber's Information
UTI	urinary tract infection
UV	ultra violet
VEGF	vascular endothelial growth factor
WCB	working cell bank
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Amgen Europe B.V. submitted on 1 December 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for MVASI, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indications:

MVASI in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum.

MVASI in combination with paclitaxel is indicated for first-line treatment of adult patients with metastatic breast cancer. For further information as to human epidermal growth factor receptor 2 (HER2) status, please refer to section 5.1.

MVASI, in addition to platinum-based chemotherapy, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology.

MVASI, in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations (see section 5.1).

MVASI in combination with interferon alfa-2a is indicated for first-line treatment of adult patients with advanced and/or metastatic renal cell cancer.

MVASI, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of adult patients with advanced (International Federation of Gynecology and Obstetrics (FIGO) stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.

MVASI, in combination with carboplatin and gemcitabine, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.

MVASI in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin is indicated for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents (see section 5.1).

MVASI, in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix (see section 5.1).

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for biosimilar medicinal products.

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

This application was submitted, in accordance with Article 82.1 of Regulation (EC) No 726/2004, as a multiple of KYOMARC simultaneously being under initial assessment. KYOMARC was subsequently withdrawn by the applicant on 17 October 2017.

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Avastin 25 mg/ml concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 01/12/2005
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation numbers: EU/1/04/300/001-002

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Avastin 25 mg/ml concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 01/12/2005
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation numbers: EU/1/04/300/001-002

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which comparability tests and studies have been conducted:

- Product name, strength, pharmaceutical form: Avastin 25 mg/ml concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 01/12/2005
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation numbers: EU/1/04/300/001-002

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 17 November 2011. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bjorg Bolstad Co-Rapporteur: Greg Markey

- The application was received by the EMA on 1 December 2016.
- The procedure started on 17 December 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 March 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 March 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 24 March 2017.
- During the meeting on 21 April 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The applicant submitted the responses to the CHMP consolidated List of Questions on 14 July 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 22 August 2017.
- During the PRAC meeting on 1 September 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 14 September 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 10 October 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 25 October 2017.
- The CHMP adopted a report on similarity of MVASI with Lynparza, Yondelis, Torisel and Zejula on 9 November 2017 (Appendix 1).
- During the meeting on 9 November 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to MVASI.

2. Scientific discussion

Problem statement

This application concerns a centralised procedure for marketing authorisation of MVASI (ABP 215) bevacizumab concentrate for solution for intravenous infusion of 25 mg/mL, as a biosimilar product to the European reference product product Avastin (EU/1/04/300/001-002).

Bevacizumab is a humanised monoclonal antibody of the immunoglobulin G1 (IgG1) subclass.

About the product

ABP 215 is a recombinant IgG1 humanised monoclonal antibody produced from Chinese hamster ovary cells. The monoclonal antibody contains murine heavy and light chain complementarity determining region sequences and human immunoglobulin G1 kappa constant region sequences. ABP 215 has the same primary structure as bevacizumab.

The primary mechanism of action of bevacizumab involves the inhibition of vascular endothelial growth factor (VEGF), which is a potent mitogen and survival factor for endothelial cells. Vascular endothelial growth factor has been shown to bind two related VEGF receptors (VEGFRs), VEGFR-1 (Fms-related tyrosine kinase 1 [Flt-1]) and VEGFR-2 (kinase insert domain receptor), expressed on vascular endothelial cells (Park et al, 1994; Waltenberger et al, 1994). When expressed alone, VEGFR-1 is unable to mediate cellular responses to VEGF and is only very weakly auto-phosphorylated following VEGF binding (Waltenberger et al, 1994).

Evidence from knockout mice and recombinant expression studies demonstrate that VEGFR-2, expressed alone, can mediate all known cellular effects of VEGF, and is thus the primary functional receptor for VEGF (Shalaby et al, 1995; Waltenberger et al, 1994). Studies comparing the dose effects of VEGF on human umbilical vein endothelial cells (which naturally express both VEGFR-1 and VEGFR-2) to cells engineered to express just one of the receptors, suggest that signalling is mediated primarily by VEGFR-2, but that heterodimers between VEGFR-1 and VEGFR-2 may be formed (Waltenberger et al, 1994).

In summary, VEGF binds with high affinity to VEGFR-1 and VEGFR-2, but only induces tyrosine kinase activity of VEGFR-2, and VEGFR-2 is sufficient to mediate VEGF mitogenic and angiogenic responses. Thus, VEGFR-2 is the primary signalling receptor for VEGF. The binding of bevacizumab to VEGF inhibits activation of VEGFR-2 and thus inhibits angiogenesis, which is required for the growth and persistence of solid tumours and their metastases. Additionally, bevacizumab has been shown to inhibit VEGF-induced cellular proliferation and vascular permeability, and normalise the vasculature, thereby potentially promoting the delivery of cytotoxic chemotherapy (Goel et al, 2011).

The Applicant claimed the same therapeutic indications and posology for the proposed biosimilar Mvasi as granted for Avastin in the European Union (EU):

- MVASI in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum.
- MVASI in combination with paclitaxel is indicated for first-line treatment of adult patients with metastatic breast cancer.

- MVASI, in addition to platinum-based chemotherapy, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology.
- MVASI, in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations.
- MVASI in combination with interferon alfa-2a is indicated for first-line treatment of adult patients with advanced and/or metastatic renal cell cancer.
- MVASI, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of adult patients with advanced (International Federation of Gynecology and Obstetrics (FIGO) stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.
- MVASI, in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents.
- MVASI in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin is indicated for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents.
- MVASI, in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix.

Type of Application and aspects on development

Development programme/compliance with CHMP guidance/scientific advice

The Applicant requested scientific advice from the CHMP on quality aspects in 2011 (EMA/CHMP/SAWP/2215/1/2011/III) regarding critical aspects of the development plan of ABP 215.

The Applicant has received EMA/CHMP scientific advice regarding analytical comparability, PK equivalence, and phase 3 clinical study in subjects with non-squamous NSCLC (Procedure No. EMEA/H/SA/2215/1/2011/III) EMA/CHMP/SAWP/298068/2015)).

CHMP guidelines

The following guidelines are considered of special interest:

Table 1: Guidelines

Guideline	Document Reference	Topic
Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues	EMEA/CHMP/BMWP/42832/2005 Rev 1, 2014	Development plan
Guideline on Similar Biological Medicinal Products	CHMP/437/04 rev 1, 2014	Development plan
Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues	EMEA/CHMP/BMWP/403543/2010	Development plan
Guideline on the investigation of bioequivalence	CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **	PK trial design
Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins	CHMP/EWP/89249/2004	PK trial design
Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins	EMEA/CHMP/BMWP/14327/2006	PK and efficacy/safety trial design
Guideline on the evaluation of anticancer medicinal products in man	EMA/CHMP/205/95/Rev. 4	Efficacy trial design
Draft Guideline on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis	CPMP/EWP/556/95 Rev. 2	Efficacy trial design
Guideline on the choice of the non-inferiority margin	EMEA/CPMP/EWP/2158/99	Efficacy trial design

2.1. Quality aspects

2.1.1. Introduction

Mvasi (ABP 215) has been developed as a biosimilar product to the reference product, Avastin (bevacizumab). Both ABP 215 and the reference product are humanized monoclonal antibodies of the IgG1 subclass expressed in Chinese hamster ovary (CHO) cells.

The finished product is supplied as a sterile, preservative-free concentrate for solution for intravenous infusion containing 25 mg/ml of bevacizumab as active substance. ABP 215 is formulated with the same excipients as the reference product, and is provided in the same pharmaceutical form and dosage strengths.

Other ingredients are: trehalose dihydrate, sodium phosphate, polysorbate 20 and water for injections.

The product is available as 4 mL solution in a vial (Type I glass) with a stopper (butyl rubber) containing 100 mg of bevacizumab and a 16 mL solution in a vial (Type I glass) with a stopper (butyl rubber) containing 400 mg of bevacizumab.

2.1.2. Active Substance

General Information

ABP 215 is a humanized monoclonal antibody of the immunoglobulin G1 (IgG1) subclass and consists of 2 heavy chains (HC), and 2 light chains (LC) of the kappa subclass. ABP 215 contains 32 total cysteine residues involved in both intrachain and interchain disulfide bonds. Each HC contains 453 amino acids with 4 intrachain disulfides. Each LC contains 214 amino acids with 2 intrachain disulfides. Each HC contains an N-linked glycan at the consensus glycosylation site on Asn^{303}. The HC C-terminal Lys^{453} is mostly removed due to the presence of carboxypeptidases during the cell culture process.

The theoretical molecular mass is 149,197 Da (glycosylated with A2G0F glycan and C-terminal lysine) and the experimental molecular mass is 149,200 Da (C-terminal lysine processed, all cysteines bridged)

ABP 215 has been developed as a biosimilar product to the reference product Avastin (bevacizumab, EMA/H/C/000582). Like bevacizumab, ABP 215 is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) cell expression system.

ABP 215 binds to human vascular endothelial growth factor A (VEGF-A) with high affinity and prevents the signalling of VEGF receptors VEGFR-1 and VEGFR-2, and heterodimers of VEGFR-1, VEGFR-2, and VEGFR-3. VEGF-A-induced signalling through these receptors results in the proliferation of vascular endothelial cells and angiogenesis. Although VEGF-A-induced angiogenesis is required for normal vascular neogenesis, skeletal growth, reproductive functions and wound repair, VEGF-A also plays a key role in pathological angiogenesis that is required for solid tumour growth and metastasis. VEGF-A antagonists have been shown to reduce pathological angiogenesis, growth and metastasis of tumours.

ABP 215 lacks effector functions such as antibody dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC).

Manufacture, characterisation and process controls

Description of the Manufacturing process

The active substance is manufactured in accordance with current good manufacturing practices (cGMP) at Amgen Thousand Oaks, USA (ATO).

Material from a single cell culture production bioreactor is harvested and purified to comprise a single lot of active substance. The process begins with thawing a working cell bank (WCB) vial. A single production lot is initiated from a single vial thaw. After the vial thaw, the process includes steps for expanding the culture to inoculate the production bioreactor. At the end of the production culture, cells and cellular debris are removed through the harvest steps.

Purification of ABP 215 is achieved through a series of chromatography, filtration, and viral inactivation steps. Product pools are held within defined hold times and temperatures prior to further processing.

The container closure system for the active substance is a 10 L polycarbonate container with a polypropylene screw thread cap and thermoplastic elastomer gasket. Specifications for the container closure components have been provided and are satisfactory.

Acceptable hold times at defined temperatures have been established for harvest and purification in-process pools. The acceptable hold times were determined in process characterization studies for chemical stability. Validation studies were also conducted to establish validated hold times based on in-process product quality and a demonstration of microbial control at the production scale. During manufacturing, the pool holds are controlled within the validated hold times through the manufacturing procedures. No reprocessing is proposed for the active substance manufacturing process.

Control of materials

All manufacturing raw materials are received, identified, sampled, quarantined, tested, labeled, and released according to established written procedures.

A listing of raw materials and process solutions, including cell culture media, stock solutions and buffers, used in the active substance manufacturing process has been provided. Compendial materials are tested to the referenced compendia. Specifications are provided for all non-compendial materials and media solutions used in the process and considered acceptable.

The production cell line was generated at Amgen. The source, history and generation of the cell substrate and cell line development was described.

Verification of the bevacizumab primary sequence was performed using analytical techniques including Edman N-terminal sequencing, liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) for peptide mapping of enzymatically cleaved product, and mass analysis of intact and reduced product by electrospray ionization time-of-flight (ESI-TOF) mass spectrometry.

The master cell bank (MCB) and working cell bank (WCB) were manufactured in compliance with current good manufacturing practices (cGMP) and tested and characterized according to ICH Q5D.

Relevant testing was performed to confirm the integrity and genetic stability of the cell line through the limit of in vitro cell age (LIVCA).

Any future WCBs will be created from a MCB vial following the submitted protocol.

Control of critical steps and intermediates

The control strategy incorporates the standard elements of the Applicant's control strategy, which is used in the control of manufacture of many of the Applicant's products. Elements include identification of Critical Quality Attributes (CQAs) by risk assessment, followed by identification of the process steps and operations which could impact these CQAs. Suitable strategies have been implemented to ensure process parameters remain within ranges which are demonstrated to not impact on the CQAs. These strategies include control of equipment and operations within pre-defined critical process parameter ranges, monitoring/control of In-process controls (IPCs) and release specifications, validation, stability, comparability etc. To ensure the suitability of the overall control strategy, a Product Quality Risk Assessment was conducted, which assesses the impact of severity, occurrence and detectability of any excursion to a CQA. The risk assessment confirms that no medium or high risk steps are identified. This risk assessment will be re-examined periodically.

IPCs are used to monitor the manufacturing process to ensure that the active substance and resulting finished product will meet quality requirements, or to monitor process consistency.

Process validation

The active substance manufacturing process was validated at ATO. Validation acceptance criteria for process parameters and performance indicators were based on reference product data, process understanding gained from prior knowledge, process characterization, and clinical manufacturing. Process validation was completed for cell culture, harvest, purification, and in-process pool holds. Validation data demonstrated that the process is controlled and reproducible while consistently producing active substance having the required quality when conducted within the defined operating ranges.

Additionally, cleaning effectiveness as well as performance over the lifetime of the chromatography resins and ultrafiltration/diafiltration (UF/DF) membranes is adequately supported by small scale studies and ongoing validation.

Data has also been presented to validate the shipping duration.

Manufacturing process development

Throughout development, no changes in scale and no significant changes to the active substance manufacturing process were made. A single site change was made between the manufacture of development and clinical lots. The proposed commercial site is the same as that used to produce the clinical lots.

The active substance was initially manufactured at Amgen Washington (AWA) using the pre-master cell bank. Material manufactured at AWA was used to establish the primary reference standard and in pre-clinical studies. The process was transferred to ATO at the same scale. With the exception of the implementation of the WCB, no changes were made to the process as a result of the transfer.

During development, a comparability study was performed to demonstrate that the clinical material manufactured at ATO was comparable to the development lots manufactured at AWA. The comparability assessment included lot release methods capable of assessing product purity and a characterization method capable of detecting differences in glycan species. All lots were tested using routine lot release methods for purity, potency, and general properties. Minor differences between the development batches and the clinical batches were observed, but concluded to be without any biological significance.

Characterisation

The elucidation of structure studies were conducted using ABP 215 active substance manufactured at ATO using the intended commercial process and scale. Characterization included biochemical studies (primary structure, glycosylation, disulfide structure, charge variants and size variants), biophysical studies (secondary structure, tertiary structure and thermal stability), biological studies (mechanism of action, including antigen specificity and Fc functionality) and forced degradation studies under specific stress conditions, to reveal potential degradation pathways and understand product quality attributes.

The primary structure was confirmed by peptide mapping and mass analysis, with 100% sequence coverage and good correlation with expected values for the polypeptide and expected glycoforms. Details have been provided for product-related substances, which are present at low levels.

Disulfide linkages were as expected, with 12 intrachain bonds and 4 interchain bonds connecting the heavy and light chains.

ABP 215 contains a single N-linked glycosylation site at Asn^{303}. Full analytical details of the glycans were provided.

Based on comprehensive characterization presented in the dossier the determined product-related impurities were identified. The product-related impurities were determined to have a potential impact on patient safety or product efficacy. The product-related impurities are present at very low levels in the active substance and are controlled to acceptable levels by the manufacturing process. Process-related impurities encompass those derived from or introduced during the active substance manufacturing process. Included are impurities from the host cell line and raw materials used during cell culture and downstream processing.

The removal of host cell protein (HCP), DNA, and residual protein A in the active substance process was evaluated in commercial-scale runs. Removal of these impurities to predefined acceptance criteria was demonstrated during challenge studies performed at small-scale during process characterization and confirmed during process validation.

Specification

Active substance specifications are given for identity, purity, potency, quantity, adventitious agents, as well as general tests. The active substance release specifications are considered acceptable.

Analytical methods

The Applicant has provided summaries of the analytical methods applied during active substance manufacture as well as detailed descriptions on how the methods are performed. Non-pharmacopoeial analytical methods have been appropriately validated.

Batch analysis

Batch analysis data have been provided for all active substance lots used during development through process validation. Fifteen lots were produced at the Amgen Washington (AWA) process development facility or the Amgen Thousand Oaks (ATO) active substance manufacturing facility. Each lot was tested to the specification in place at the time of testing. The results confirm consistency of the manufacturing process.

Reference materials

The primary and working reference standards are well characterized. An acceptable study protocol is in place for control of the stability of the reference standard. Forty-eight months data are currently available from real-time studies at -70^{o}C ± 10^{o}C supporting that the primary reference standard is stable. Additionally, results from a one month real-time stability study have been provided, demonstrating stability of the reference standard when held at 2^{o}C to 8^{o}C for up to 1 month.

A protocol for qualification of future reference standards has been provided, including studies for monitoring the stability.

Stability

An expiry period has been proposed for the active substance stored at the recommended storage temperature.

Stability studies were conducted at the recommended storage temperature to support the expiry period. The studies were performed in accordance with ICH Q5C. The chosen stability parameters for the long-term studies were considered acceptable and included tests for appearance, purity, potency and pH.

All supporting, primary, and production lots were manufactured using the intended commercial active substance process. Stability containers were smaller than (but otherwise identical to) the container closure system used in manufacturing, comprising a 30 mL polycarbonate bottle with a polypropylene screw cap and a thermoplastic elastomer gasket.

For the long-term stability study no major trends were observed.

Stability studies were conducted at accelerated and stressed conditions to compare relative rates of degradation, assess the effect of temperature stress on the product, and support potential temperature excursions. Stability data at the accelerated storage conditions demonstrate that the active substance remains stable under accelerated conditions. Stability data at the stressed storage condition demonstrate that the active substance remains stable under stressed conditions.

2.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Description and composition of the finished product

The finished product is supplied as a sterile, preservative-free concentrate for solution for intravenous infusion containing 25 mg/ml of bevacizumab. The product is available as a 4 mL solution in a vial containing 100 mg of bevacizumab and as a 16 mL solution in a vial containing 400 mg of bevacizumab. The excipients (trehalose dihydrate, sodium phosphate, polysorbate 20, and water for injections) are well-known and comply with the Ph Eur. The container closure system consists of a Type I glass vial with a fluoropolymer laminated elastomeric stopper and an aluminum seal with flip-off cap. The vial, stopper and seal components are compliant with appropriate Ph Eur monographs for primary containers and closures.

No formula overages are included. The vials are filled to ensure a deliverable volume of 4 mL for the 100 mg presentation and 16 mL for the 400 mg presentation.

Pharmaceutical development

The finished product was developed to have the same formulation, route of administration, dosage form and strength as the reference product Avastin.

The active substance and finished product have an identical formulation. Compatibility of the active substance with the excipients has been confirmed.

Formulation studies were conducted to evaluate finished product stability. The results demonstrated that the finished product is physically and chemically stable in the selected formulation.

Manufacturing process development

The finished product manufacturing process was characterized to develop a comprehensive understanding in order to consistently deliver the required finished product quality. The process design approach was based on an evaluation of existing knowledge from a variety of sources, including reference product data, prior knowledge from other platform monoclonal antibody processes, ABP 215 process development studies and manufacturing experience, and the results of process risk assessments. The comprehensive process understanding gained from these evaluations and studies was used to establish process parameters for each

process step and in-process controls (IPCs) for demonstrating acceptable process performance during routine manufacturing operations. Process characterization studies were performed.

Acceptable ranges for the process parameters were established. Parameters were assessed for criticality based on their potential to impact product quality. When operated within the process parameter acceptable ranges, the process delivers acceptable quality and process performance.

A manufacturing site change was made between clinical and commercial manufacturing.

Analytical comparability was demonstrated between finished product manufactured at the two manufacturing sites using biochemical, biophysical, and biological analytical methods including methods routinely used for lot release and product characterisation. The comparability assessment also included an evaluation of accelerated stability data. The results demonstrated that the finished products were comparable.

Analytical comparability assessments were also performed to evaluate the introduction of the 100 mg vial during clinical development. The 100 mg vial was shown to be comparable to the 400 mg vial.

Manufacture of the product and process controls

The finished product manufacturing process includes active substance thaw, active substance hold, active substance pooling and mixing, bioburden reduction filtration, filtered formulated active substance hold, filtered formulated active substance warming, sterile filtration, aseptic filling, stoppering and sealing, inspection, and storage. Reprocessing is not currently proposed during manufacturing of ABP 215 finished product.

IPCs are used to ensure process consistency and product quality during the manufacture of the vials. The critical IPCs with action or rejection limits for the finished product manufacturing process have been presented.

A comprehensive microbial control strategy has been implemented to minimize the potential for introduction and proliferation of microbial contaminants in order to ensure the production of sterile product.

The finished product process validation strategy was designed to demonstrate that the manufacturing process is controlled and reproducible, consistently yielding finished product with the required product quality.

The finished product manufacturing process was validated. Aseptic process validation, media fill validation, cleaning validation, filter validation, and equipment sterilization validation were performed in support of the finished product process validation. Validation acceptance criteria for process parameters and performance indicators were based on process understanding gained from process characterisation and clinical manufacturing. Three consecutive finished product lots were manufactured for both the 100 mg and 400 mg vial. Batch analysis data for these lots demonstrated batch to batch consistency at the commercial facility with the commercial process.

The finished product can be transported by air, ground, and ocean modes between manufacturing, packaging, and distribution sites. Finished product exposed to transport conditions of vibration, pressure, and shock events has been evaluated, and the results confirm that product quality is maintained when transported.

Product specification

The finished product specification applies to both the 100 and 400 mg presentations. The two presentations are analytically comparable. Therefore, the same specification acceptance criteria are used for assessing product quality, with the exception of volume.

Development of the finished product specification was performed in accordance with *ICH Q6B, Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* and *ICH Q8, Pharmaceutical Development.*

Information gained from characterisation studies, scientific understanding of product quality attributes, as well as prior knowledge derived from process characterisation of other monoclonal antibodies, were used to determine the potential impact of quality attributes of the product on patient safety and product efficacy.

Relevant tests have been included in the finished product specification to control appearance, identity, purity, potency and quantity. The product-related impurities are present at very low levels in the finished product and are controlled to acceptable levels by the manufacturing process. The composition of the finished product is identical to that of the active substance and no new impurities are introduced as a result of the finished product manufacture.

The data set used to calculate and establish the acceptance limits included release testing results from the finished product manufactured at the clinical and commercial manufacturing sites, as well as stability data from finished product lots held at the recommended storage conditions.

Analytical methods

Validation summaries for analytical procedures used to test the finished product have been provided.

Batch analysis

Batch analysis data have been provided for all finished product lots manufactured during development through process validation, covering both the 100 mg and 400 mg presentations.

The batch analysis data presented demonstrated that the proposed finished product release limits were met for all batches and confirmed product reproducibility.

Reference materials

Please see the active substance section. The same reference standard is used for testing both the active substance and finished product.

Stability of the product

A shelf life of 24 months has been proposed for the finished product stored at the recommended storage temperature of 2°C to 8°C.

The stability studies were performed in accordance with ICH Q5C.

The supporting stability lots were manufactured using active substance manufactured using the commercial process. Real time data covering up to 48 months was provided.

Primary stability lots were manufactured using active substance manufactured using the commercial process and scale at ATO. Real time data covering up to 48 months was provided.

Production lots were manufactured using the commercial process and scale and with active substance manufactured using the commercial process and scale at ATO. Real time data covering up to 12 months was provided.

The primary container closure system used for finished product lots in the stability program was identical to those used in clinical trial and proposed for commercial distribution.

Stability studies at elevated temperatures were also conducted to assess the effect of accelerated stress conditions to confirm relative degradation rates between supporting, primary, and production/comparability finished product lots. Additionally, experimental studies were performed to assess the effect of other storage conditions (e.g. temperature cycling and light) on the finished product.

Results of these studies, together with results from the accelerated and stressed stability studies, demonstrate that the finished product is stable in the primary container, protected from light, under conditions that may be encountered during transport, storage, handling, and use.

As the photostability studies demonstrated that the product is sensitive to light, the SmPC states that the vial should be kept in the outer carton in order to protect from light.

Data provided demonstrate that the finished product is physically stable in 0.9% saline diluent for intravenous administration for 48 hours at 2°C to 30°C and is compatible with commonly used IV bags and tubing materials.

Based on the data provided a shelf life of 24 months is accepted.

Analytical similarity assessment

Mvasi (ABP 215) has been developed as a biosimilar product to the reference product Avastin (EMEA/H/C/000582, Marketing Authorisation held by Roche).

The Applicant performed a comprehensive analytical similarity assessment which included comparative evaluations of biological activity, primary structure, higher order structure, particles and aggregates, product-related substances and impurities, thermal stability and degradation studies, general properties, and process-related impurities using state-of-the-art methods.

The reference product is supplied in 100 mg and 400 mg preservative free, single-use vials to deliver 4 mL or 16 mL of bevacizumab (25 mg/mL), respectively. For attributes not impacted by the presentation, results were pooled from both presentations to establish the reference product profile for analytical similarity assessment. For volume, which is impacted by the presentation, results were presented separately for each presentation.

Generally, the approaches used for establishment of the biosimilarity assessment criteria were considered acceptable. According to the proposed criteria, a conclusion on comparability was made if > 90% of individual batches of biosimilar product fell within the calculated range of mean ± 3 SD for the reference product. This approach could easily lead to acceptance criteria that are too wide to conclude on similarity. However, as data from the analysis of individual batches were provided, an assessment can be made independently of the statistical model used. For attributes where a change over time was observed when stored at the recommended storage condition, values were adjusted for material age prior to calculating the range. The Applicant has provided data demonstrating suitability of the model used including goodness-of-fit and linearity.

The outcome of the physicochemical and biological comparability exercise between Mvasi and Avastin is summarised in the tables below.

Table 2: Analytical Similarity Assessment Results for Functional Activity Assays

Method	Relevant Activity	Key Findings
Fab-mediated Activities		
Binding to VEGF	VEGF	Similar binding
Neutralization of VEGF-mediated proliferation in HUVEC (potency)	VEGF	Similar potency
On and off bind rates (VEGF)	VEGF	Similar rates
Binding to VEGF isoforms	$VEGF_{121}$ and $VEGF_{165}$	Similar binding
Inhibition of VEGFR-2 RTK autophosphorylation	VEGF	Similar inhibition
Specificity by VEGFR-2 RTK autophosphorylation	VEGF-C and VEGF-D	Similar specificity
Fc-mediated Characterization		
Binding to FcRn	FcR	Similar binding
Binding to FcγRIa	FcR	Similar binding
Binding to FcγRIIa (131H)	FcR	Similar binding
Binding to FcγRIIb	FcR	Similar binding
Binding to FcγRIIIa (158V)	FcR	Similar binding
Binding to FcγRIIIa (158F)	FcR	Similar binding
Binding to FcγRIIIb	FcR	Slightly higher relative binding activity for MVASI
Binding to C1q	C1q	Similar binding
Fab- and Fc-mediated Characterization		
Lack of ADCC activity	VEGF and FcR	Similar lack of activity
Lack of CDC activity	VEGF and C1q	Similar lack of activity

ADCC = antibody-dependent cell-mediated cytotoxicity; C1q = first subcomponent of the C1 complex of the classical pathway of complement activation; CDC = complement-dependent cytotoxicity; F = phenylalanine; Fc = fragment crystallizable; FcR = Fc receptor; FcRn = neonatal Fc receptor; FcγRIa = Fc gamma receptor Type Ia; FcγRIIa = Fc gamma receptor Type IIa; FcγRIIb = Fc gamma receptor Type IIb; FcγRIIIa = Fc gamma receptor Type IIIa; FcγRIIIb = Fc gamma receptor Type IIIb; H = histidine; HUVEC = human umbilical vein endothelial cells; RTK = receptor tyrosine kinase; V = valine; VEGF = vascular endothelial growth factor; $VEGF_{121}$ = vascular endothelial growth factor isoform 121; $VEGF_{165}$ = vascular endothelial growth factor isoform 165; VEGF-C = vascular endothelial growth factor type C; VEGF-D = vascular endothelial growth factor type D; VEGFR-2 = vascular endothelial growth factor receptor 2.

Table 3: Analytical Similarity Assessment Results for Structural and Purity Characteristics

Category	Analytical Testing and Parameter	Key Findings
Primary Structure	Intact molecular mass: Profile	Similar profile
	Intact molecular mass: Molecular weight	Similar molecular weight
	Reduced and deglycosylated molecular masses of HC and LC: Profile	Similar profile
	Reduced and deglycosylated molecular masses of HC and LC: Molecular weight	Similar molecular weight
	Reduced peptide map: Profile	Similar profile
	Reduced peptide map: amino acid sequence	Similar amino acid sequence
	Non-reduced peptide map: Profile	Similar profile
	Non-reduced peptide map: Disulfide structure	Similar disulfide structure
	Glycan map: Profile	Similar profile
	Glycan map: % high mannose	Minor quantitative differences in specific glycans
	Glycan map: % galactosylation	
	Glycan map: % afucosylation	
	Glycan map: % sialylation	Similar sialylation
	cIEF: Profile	Similar profile
	cIEF: Isoelectric point	Similar isoelectric point
	Extinction coefficient	Similar extinction coefficient
	Identity by ELISA	Same identity
Higher Order Structure	FTIR: Spectral similarity	Similar FTIR spectra
	FTIR: Profile	Similar profile
	Near UV CD: Spectral similarity	Similar near UV CD spectra
	Near UV CD: Profile	Similar profile
	DSC: Profile	Similar profile
	DSC: T_{m1}	Similar T_{m1}
	DSC: T_{m2}	Similar T_{m2}

Particles and Aggregates	HIAC: ≥ 2 μm particles ≥ 5 μm particles ≥ 10 μm particles ≥ 25 μm particles	Similar particle levels
	MFI: ≥ 5 μm particles	Similar particle levels
	MFI: ≥ 5 μm non-spherical particles	Similar non-spherical particle levels
	FFF: Submicron particles	Similar submicron particle levels
	DLS: Submicron particles	Similar submicron particle levels
	AUC-SV: Monomer (%)	Similar monomer
	AUC-SV: Profile	Similar profile
	SE-HPLC-LS: Molar mass	Similar molar mass
Product-related Substances and Impurities	SE-HPLC: Profile	Similar profile
	SE-HPLC: HMW	Slightly lower levels of high molecular weight species in MVASI
	rCE-SDS: Profile	Similar profile
	rCE-SDS: HC+LC	Higher glycan occupancy and lower levels of fragmented species in MVASI
	rCE-SDS: NGHC	
	rCE-SDS: LMW + MMW	
	nrCE-SDS: Profile	Similar profile
	nrCE-SDS: Main peak	Minor differences in partially reduced species
	nrCE-SDS: Pre-peaks	
	CEX-HPLC: Profile	Similar profile
	CEX-HPLC: Acidic peaks	Lower amounts of acidic variants and slightly higher amounts of basic variants in MVASI
	CEX-HPLC: Main peak	
	CEX-HPLC: Basic peaks	
Thermal Stability and Degradation	50°C Forced degradation	Similar forced degradation profile
	40°C Stressed stability	Similar stressed stability profile
	25°C Accelerated stability	Similar accelerated stability profile
General Properties	Protein concentration (mg/mL)	Similar protein concentration
	Volume	Similar volume
	Osmolality	Similar osmolality
	pH	Similar pH
	Appearance	Similar appearance
	Color	Similar color
	Clarity	Similar clarity

Process related Impurities	HCP- ELISA	Similar HCP levels
	HCP analysis by LC-MS	Similar HCP levels
	Protein A - ELISA	Similar protein A levels
	Residual DNA - qPCR	Similar DNA levels

2D-DIGE = 2 dimensional in-gel electrophoresis; AUC-SV = analytical ultracentrifugation sedimentation velocity; CEX-HPLC = cation exchange high performance liquid chromatography; cIEF = capillary isoelectric focusing; DLS = dynamic light scattering; DSC = differential scanning calorimetry; ELISA = enzyme linked immunosorbent assay; FFF = field flow fractionation; FTIR = fourier transform infrared spectroscopy; HC = heavy chain; HCP = host cell protein; HIAC = high accuracy light obscuration particle counting; HMW = high molecular weight; LC = light chain; LC-MS = liquid chromatography mass spectrometry; LMW = low molecular weight; LOQ = limit of quantitation; MFI = micro flow imaging; MMW = mid molecular weight; NGHC = non-glycosylated heavy chain; nrCE-SDS = non reduced capillary electrophoresis - sodium dodecyl sulfate; pI = isoelectric point; qPCR = quantitative polymerase chain reaction; rCE-SDS = reduced capillary electrophoresis - sodium dodecyl sulfate; SE-HPLC = size exclusion high performance liquid chromatography; SE-HPLC-LS = size exclusion high performance liquid chromatography with light scattering detection; UV CD = ultraviolet circular dichroism.

Similarity with regards to the biological activity has been studied by inhibition of proliferation in human umbilical vein endothelial cells (HUVEC), binding to the target (VEGF-A), binding kinetics for VEGF 121, and a comparison of the binding to the common isoforms VEGF 121 and VEGF 165. Blockade of signaling downstream of the receptor VEGFR-2, was evaluated using a receptor tyrosine kinase (RTK) assay in HUVEC. The specificity of ABP 215 and the reference product for VEGF-A was demonstrated using the RTK assay by substituting VEGF-C or VEGF-D. FcRn binding was studied using a competitive AlphaScreen binding assay. Fc receptor and C1q binding has been studied as well as lack of ADCC and CDC activity. The methods used were considered appropriate and the data presented indicate that ABP 215 and the reference product have similar biological activity.

Testing for the general properties protein concentration, volume, osmolality, pH, appearance, colour and clarity have been performed. Slight differences were observed between the reference product and ABP 215 regarding colour and visible particles, but these are not expected to have any clinical impact and are therefore considered acceptable.

Higher order structure has been studied by FTIR spectroscopy, Near Ultraviolet Circular Dichroism and differential scanning calorimetry, and similarity is considered demonstrated. The levels of subvisible particles were determined using HIAC and MFI methods. The HIAC method measures ≥2 µm, ≥ 5 µm, ≥10 µm, and ≥25 µm size particles. The Applicant concluded that ABP 215 has similarly low levels of HIAC subvisible particles compared to the reference product.

The analytical similarity of the primary structure of ABP 215 and the reference product was established through the use of several complementary characterization methods, which include whole protein mass analysis, reduced and deglycosylated heavy chain and light chain mass analyses, reduced and non-reduced peptide mapping, glycan mapping, comparison of isoelectric points, extinction coefficients, and confirmation of identity using an immunoassay. The presented data revealed minor analytical differences in biochemical attributes between ABP 215 and the reference product. These differences have been justified and do not have any clinical significance.

Process-related impurities such as host cell protein (HCP), host cell DNA, and leached protein A were characterized. Results provided support the conclusion that ABP 215 has similarly low levels of process-related impurities compared to the reference product.

Product-related substances and impurities of ABP 215 and the reference product were assessed using a combination of methods that evaluate size and charge variants. Physicochemical properties of size variants were assessed by size exclusion high performance liquid chromatography (SE-HPLC), reduced capillary electrophoresis-sodium dodecyl sulfate (rCE-SDS), and non-reduced capillary electrophoresis-sodium dodecyl sulfate (nrCE-SDS). Additionally, potential levels of free thiol were assessed by nrCE-SDS. Charge variants were assessed by cation exchange high performance liquid chromatography (CEX-HPLC). The SE-HPLC profiles indicated slightly lower levels of HMW species for ABP 215 as compared to the reference product, which is acceptable and in line with guidance. Data from the rCE-SDS analysis demonstrated that ABP 215 has slightly higher levels of % heavy chain and light chain (HC + LC), lower levels of % non-glycosylated heavy chain (NGHC) due to more complete glycosylation at the Asn^{303} glycosylation site on the HC, and slightly lower levels of fragment (measured as % LMW + MMW) as compared to the reference product. However, no impact was observed on the biological activity. The nrCE-SDS purity profile indicated slightly higher level of % main peak and lower level of % pre-peaks as compared to the reference product, except for one batch which fell just below the presented comparability range. Furthermore, charge variants assessed by CEX-HPLC demonstrate that ABP 215 and the reference product have a similar purity profile for CEX-HPLC, although ABP 215 is projected to have lower levels of acidic peaks at 24 months compared to the reference product. ABP 215 is also projected to have a slightly higher level of basic peak at 24 months compared to the reference product. Differences in C-terminal lysine is not expected to have any clinical impact, since C-terminal lysine is rapidly removed in serum.

Thermal stability and degradation studies have been performed indicating similar degradation profiles for ABP 215 and reference product.

Data was also provided to demonstrate that US batches can be considered representative of EU batches. However, the pivotal clinical data to support the MAA was generated with Avastin sourced in the EU.

In general, as an overall comment to the analytical similarity assessment, some minor analytical differences in the biochemical attributes have been observed between ABP 215 and the reference product. These minor differences have been evaluated and it has been concluded that they have no clinical relevance or impact on the biological activity of the product. Overall, it can be concluded that the data demonstrate that ABP 215 is analytically similar to the reference product.

Adventitious agents

The Applicant's viral safety program minimizes the potential for introduction of adventitious virus into the ABP 215 manufacturing process and includes the following:

- Master and working cell banks have been extensively tested and found to be free of detectable adventitious agents.
- Raw materials have appropriate certification.

An assessment of risk for transmissible spongiform encephalopathy (TSE) transmission was performed on all raw materials from transfection of the cell line through fill and finish of the finished product. Materials not directly used in the process, but which may come into contact with the product during manufacturing or primary packaging, were also identified and assessed.

The testing of the cell banks for virus contamination is considered adequate. No adventitious viruses have been detected, with the exception of expected A- and C-type retrovirus-like particles, which are non-infectious and typical of the parental CHO cell line.

The purification process includes dedicated steps that provide inactivation and removal of viruses. Additional viral clearance by the process is afforded by the virus removal capability of the chromatography steps. The capacity of the manufacturing process for removal/inactivation of viral contamination is considered acceptable. Viral clearance assessments utilized both non-enveloped and enveloped model viruses. Reduction factors are satisfactory.

2.1.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The Applicant has successfully demonstrated that ABP 215 is analytically similar to the reference product Avastin.

2.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

The Applicant has successfully demonstrated that ABP 215 is analytically similar to the reference product Avastin.

2.2. Non-clinical aspects

2.2.1. Introduction

The applicant presented *in vitro* pharmacology studies (eg VEGF-A binding; FcRn binding) with bevacizumab (Motanga) and bevacizumab (Avastin) and *in vivo* studies which assessed activity in vascular permeability and anti-tumour activity in xenograft experiments in mice. The PK of ABP 215 versus bevacizumab (US) was characterized in a non-GLP, single-dose study in rats and the TK of ABP 215 versus bevacizumab (US) was characterized in a GLP-compliant, multiple-dose toxicology study in cynomolgus monkey.

A 4-week repeat-dose toxicity study was conducted with ABP 215 and bevacizumab (US) in cynomolgus monkeys.

2.2.2. Pharmacology

Primary pharmacodynamic studies

In vitro

Fab-related similarity studies were conducted with ABP 215, bevacizumab (EU) and bevacizumab (US). The key findings for similarity evaluation between ABP 215 and bevacizumab (EU) is presented in Table 4.

Table 4: Fab-related similarity studies with ABP 215 and bevacizumab (EU)

Assay title (method)	Key findings
Inhibition of proliferation of HUVEC cells	The % relative potency of ABP 215 is similar to bevacizumab (EU)
Binding to VEGF-A (ELISA)	The binding activity of ABP 215 was similar to bevacizumab (EU)
Binding to VEGF-A_{121} (SPR)	k_a, k_d, and K_D of all ABP 215 lots were similar to the bevacizumab (EU) lots
Binding to VEGF-A isoforms (SPR)	The representative overlay of the VEGF-A isoform binding sensograms supports similar binding to the 2 predominant isoforms of VEGF-A, VEGF-A_{121} and VEGF-A_{165}, as compared to bevacizumab (EU).
Inhibition of VEGF-A-mediated VEGFR-2 autophosphorylation (ECL)	Similar inhibition of VEGF-A mediated VEGFR-2 auto-phosphorylation as compared to bevacizumab (EU). No inhibitory activity when using VEGF-C or VEGF-D
Specificity to VEGF-A by VEGFR-2 autophosphorylation	Neither ABP 215 nor bevacizumab showed autophosphorylation with VEGF-C or VEGF-D

Fc-related similarity studies were conducted with ABP 215, bevacizumab (EU) and bevacizumab (US). The key findings for similarity evaluation between ABP 215 and bevacizumab (EU) is presented in Table 5. ADCP-activity was not evaluated, as the results from both the ADCC and CDC assays demonstrated that there was no effector functions mediated by the Fc portion of ABP 215 or bevacizumab and no significant differences in binding to either FcRγIIa or FcRγIIIb were observed for ABP 215 compared to bevacizumab.

Table 5: Fc-related similarity studies with ABP 215 and bevacizumab (EU)

Assay title (method)	Key findings
Binding to FcRn (AlphaScreen)	The binding activity of ABP 215 was similar to bevacizumab (EU)
Binding to FcγRIa (AlphaLISA)	ABP 215 has similar relative FcγRIa binding compared to bevacizumab (EU)
Binding to FcγRIIa (131H) (SPR)	ABP 215 has similar relative FcγRIIa (131H) binding compared to bevacizumab (EU)
Binding to FcγRIIb (SPR)	ABP 215 has similar relative FcγRIIb binding compared to bevacizumab (EU)
Binding to FcγRIIIa (158V) (AlphaLISA)	The binding activity of ABP 215 was similar to bevacizumab (EU)
Binding to FcγRIIIa (158F) (AlphaLISA)	The binding activity of ABP was similar to bevacizumab (EU)
Binding to FcγRIIIb (SPR)	ABP 215 had slightly higher relative binding activity to FcγRIIIb as compared to bevacizumab (EU).
Binding to C1q	The binding activity of ABP 215 was similar to

(ELISA)	bevacizumab (EU)
ADCC-activity DLD-1 cells, Calu-6 cells, SKOV3 cells	Both ABP 215 and bevacizumab (EU) showed a similar lack of ADCC activity on the VEGF-expressing DLD-1 and Calu-6 tumour cell lines, and the VEGF-A expressing SKOV3 cell lines.
CDC-activity in DLD-1 cells, Calu-6 cells, SKOV3 cells	Both ABP 215 and bevacizumab (EU) showed a similar lack of CDC activity on the VEGF-expressing DLD-1 and Calu-6 tumour cell lines, and the VEGF-A expressing SKOV3 cell lines.

In vivo

Bevacizumab has been extensively evaluated in a number of studies, including a range of tumour xenograft models, demonstrating tumour growth inhibition, reduced microvessel density and decreased vascular tortuosity and permeability.

Two xenograft tumour models were used to compare the effects of ABP 215 and bevacizumab (US) on tumour growth and tumour vasculature. Data from these xenograft models showed that ABP 215 and bevacizumab (US) are similarly able to inhibit tumour growth and decrease vascular permeability. Furthermore, the results suggest that ABP 215 inhibits tumour growth in a manner similar to bevacizumab (US) and consistent with the known bevacizumab MOA.

Effect of ABP 215 and bevacizumab (US) treatment on tumour growth in an A431 tumour xenograft model in female athymic nude mice (study ID R20120191)

Athymic nude mice (10 females/group) were injected subcutaneously (SC) with A431 tumour cells at a concentration of 5 x 10^6 cells per mouse. Eight days later, bevacizumab (US) or ABP 215 was administered by intraperitoneal (IP) injection at doses of 10 or 100 µg twice weekly for 12 days. Tumour sizes and body weights were measured twice per week.

ABP 215 and bevacizumab (US) both significantly inhibited tumour growth when compared to the control group (IgG1) (see Figure 1). At both dose levels, ABP 215 inhibited tumour growth similarly to bevacizumab (US), with no observed statistical differences (p = 0.34 for the 10-µg dose and p = 0.16 for the 100-µg dose). There was no body weight loss in any of the treatment groups.

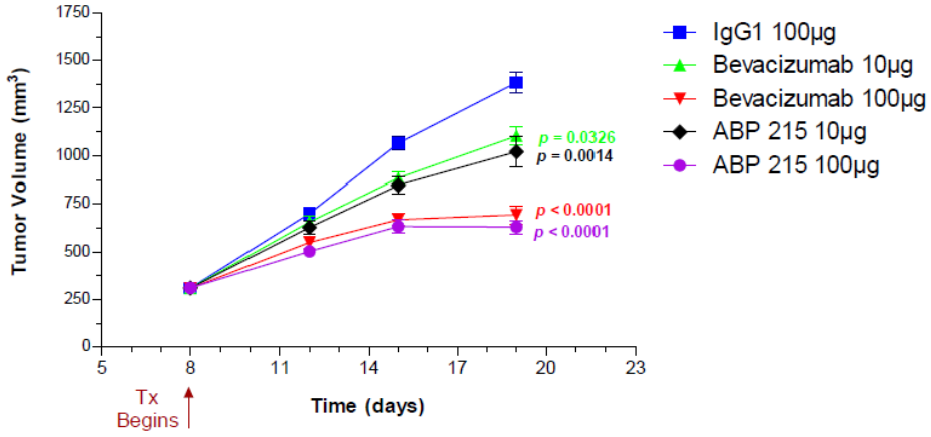


Figure 1: Effect of ABP 215 and Bevacizumab (US) on A431 Tumour Growth

Effect of bevacizumab (US) and ABP 215 treatment on A421 tumour xenograft growth and CD31 staining of vasculature in female athymic nude mice (study ID R20120192)

ABP 215 and bevacizumab (US) were evaluated for their ability to inhibit tumour-induced vascularization, as measured by CD31 staining (CD31 is expressed on the endothelial cell surface). Athymic nude mice (10 females/group) were injected with 5 × 10^6 cells/mL A431 cells in the right flank. Eight days later, ABP 215 or bevacizumab (US) was administered ip at 100 mg, twice per week. Tumour sizes and body weights were measured twice per week. After 1 week of treatment (2 doses), tumours were removed, sectioned, and stained for CD31. CD31 is expressed on the endothelial cell surface, and blood vessel area (% CD31+) was measured as a percentage of tissue area.

Results are presented in Figure 2. ABP 215 and bevacizumab at 100 µg significantly inhibited tumour growth when compared to vehicle resulting in 51% TGI. There was no body weight loss in either of the treatment groups. Both ABP 215 and bevacizumab (US) resulted in a significant and similar decrease in vessel area compared with control (IgG1), as measured by CD31 staining.

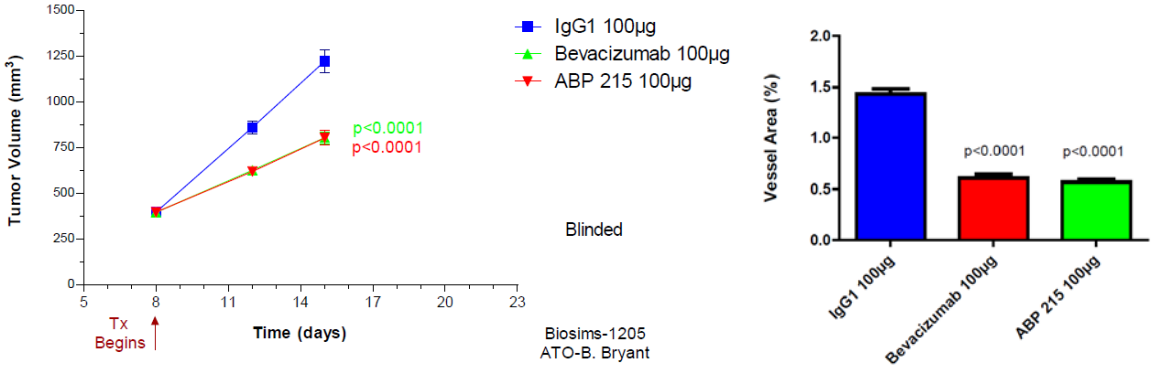


Figure 2: Effect of bevacizumab (US) and ABP 215 on A431 tumour growth (left) and vessel area (right)

A431 cells (5 x 10^6) were implanted subcutaneously into the right flank of female athymic nude mice (n = 10 per group). Tumors were measured twice per week. Treatment began on day 8 when tumors had reached ~80 mm³. Mice were dosed by IP twice per week for 1 week. Data represent mean ±SE for each group. p values correspond to statistical differences between ABP 215 and bevacizumab groups compared to the IgG1 control group, as determined by ANOVA followed by Dunnett's post hoc test.

Effect of bevacizumab (US) and ABP 215 treatment on tumour growth in a Colo205 tumour xenograft model in female athymic nude mice (study ID R20130003)

Athymic nude mice (10 females/group) were injected SC with Colo205 tumour cells at a concentration of 2 × 10^6 cells per mouse. Ten days later, ABP 215 or bevacizumab (US) was administered by IP injection at 10 or 100 µg twice weekly for 10 days. Tumour sizes and body weights were measured twice per week.

ABP 215, at both dose levels, inhibited tumour growth similarly to bevacizumab (US) (see Figure 3), with no observed statistical difference (p = 0.50 for the 10-µg dose and p = 0.95 for the 100-µg dose); ABP 215 and bevacizumab (US) significantly inhibited tumour growth when compared to the control group (IgG1). There was no body weight loss in any of the treatment groups.

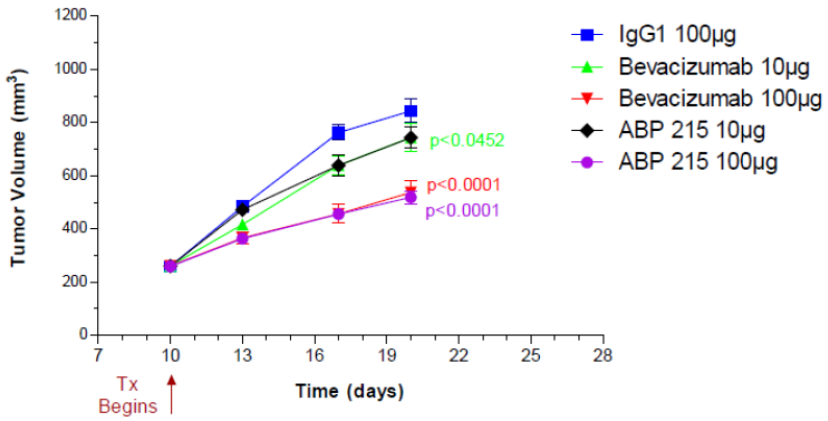


Figure 3: Effect of bevacizumab (US) and ABP 215 on Colo205 tumour growth

Effect of bevacizumab (US) and ABP 215 treatment on Colo205 tumour xenograft growth and CD31 staining of vasculature in female athymic nude mice (study ID R2013002)

ABP 215 and bevacizumab (US) were evaluated for their ability to inhibit tumour-induced vascularization, as measured by CD31 staining. Athymic nude mice (10 females/group) were injected with 5 × 10^6 cells/mL Colo205 cells in the right flank. Ten days later, ABP 215 or bevacizumab (US) was administered by IP injection at 100 µg twice weekly for 1 week. Tumour volume and body weight were measured twice per week. Tumours were collected for CD31 staining and vessel area analysis. Blood vessel area (% $CD31^+$) was measured as a percentage of tissue area.

Results are presented in Figure 4. Bevacizumab and ABP 215 treatment inhibited growth of Colo205 xenograft tumours. Both treatment groups showed statistically decreased vessel area as measured by CD31 staining. There was no body weight loss in any of the treatment groups.

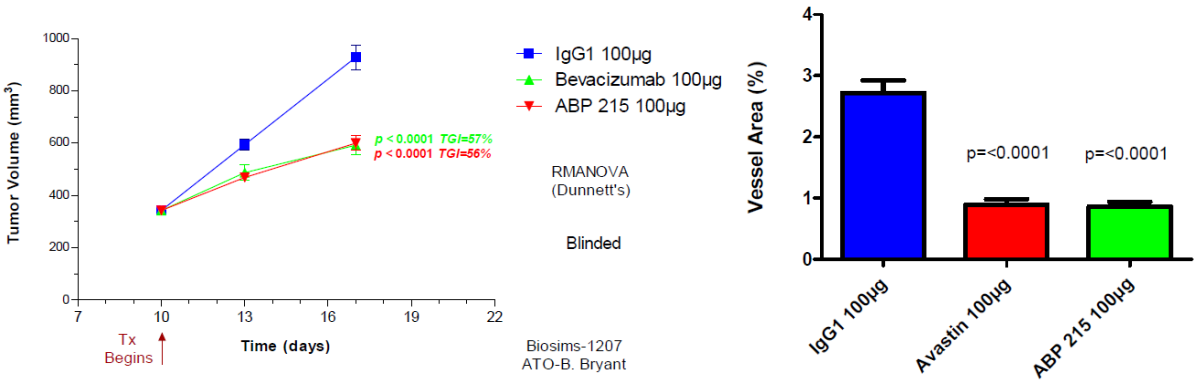


Figure 4: Effect of bevacizumab (US) and ABP 215 on Colo205 tumour growth (left) and vessel area (right)

Effect of ABP215 compared to bevacizumab (US) on VEGF-induced vascular permeability in female athymic mouse skin (study ID R20130024)

To compare ABP 215 and bevacizumab in their ability to prevent VEGF-induced vascular permeability in mouse skin, human embryonic kidney (HEK) cells transfected with recombinant human (rhu) VEGF were

used. Briefly, on day 1, groups of athymic nude mice were injected IP with 100 µg of isotype control (IgG1); 3, 10, 30, or 100 µg of ABP 215; or 3, 10, 30, or 100 µg of bevacizumab (US). On day 2, the mice were injected SC on the ventral surface with 1×10^5 HEK cells transfected with either empty vector or vector containing the sequence for rhu VEGF. On day 3, the mice were IV injected with Evans Blue dye to quantify the level of vascular permeability via spectrophotometry.

Results are presented in Figure 5. ABP 215 inhibits rhu VEGF-induced vascular permeability in mouse skin vasculature in a similar fashion to bevacizumab (US). Although there appears to be a difference in permeability between ABP 215 and bevacizumab (US) at 3 µg dose level, this difference is attributed to assay variability at low dose levels.

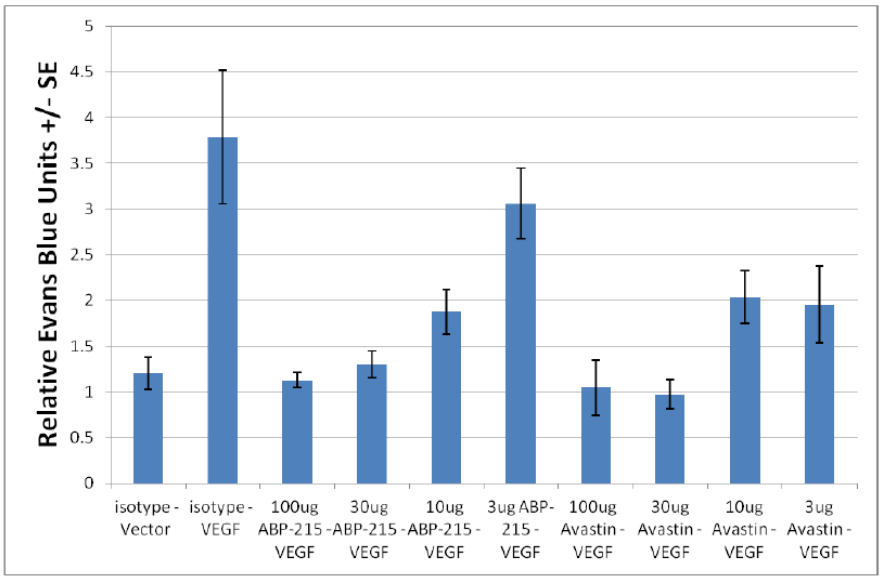


Figure 5: ABP 215 and Avastin (bevacizumab (US)) prevent VEGF induced vascular permeability in a similar fashion

Secondary pharmacodynamic studies

No studies were conducted (see discussion on non-clinical aspects).

Safety pharmacology programme

No dedicated studies were conducted (see discussion on non-clinical aspects).

Pharmacodynamic drug interactions

No studies were conducted (see discussion on non-clinical aspects).

2.2.3. Pharmacokinetics

The PK of ABP 215 versus bevacizumab (US) was characterized in a non-GLP, single-dose study in rats and the TK of ABP 215 versus bevacizumab (US) was characterized in a GLP-compliant, multiple-dose toxicology study in cynomolgus monkey.

PK study of bevacizumab and high-mannose variant ABP 215 following IV administration of a single 1 mg/kg dose to male Sprague-Dawley rats with cross-over satellite groups (study ID 114878, non-GLP)

Male SD-rats were assigned to 2 groups of 12 rats and received a single IV injection of 1 mg/kg ABP 215 or 1 mg/kg bevacizumab (US) on day 0. On day 21, 4 rats from each group were crossed over to receive a single IV 1-mg/kg dose of the alternate treatment to the one received initially. Serum samples were collected from all animals for PK analysis on day 0 and day 21, using the ELISA method.

Following IV administration on day 0, ABP 215 serum concentration profiles were similar to those from bevacizumab (US) treatment groups (see Table 6). On Day 21, 4 rats from each treatment group were

crossed over and received a single IV dose of the alternate test article to the one their received initially, i.e. initial dose with ABP 215 and subsequent dose with bevacizumab. A slight accumulation in exposure was noted in both groups since the bioanalytical assay detects both ABP 215 and bevacizumab.

Table 6: Mean (SD) pharmacokinetic parameter estimate of ABP 215 or bevacizumab (US) on Day 0 and Day 21 after IV administration of 1 mg/kg to rats

Treatment (Group)	Day	N	t_{max} (hr)[a]	C_{max} (µg/mL)	C_0 (µg/mL)	AUC_{0-504} (µg•hr/mL)	CL_{504} (mL/hr/kg)
ABP 215 (group 1)	0	12	0.25 (0.25-1.00)	22.3 (3.68)	23.2 (4.13)	2800 (352)	0.362 (0.0454)
Bevacizumab (US) (group 2)	0	12	0.25 (0.25-0.25)	23.9 (2.78)	25.2 (3.11)	3090 (327)	0.327 (0.0330)
ABP 215 (group 1a)	21	4	0.25 (0.25-0.25)	30.1 (1.82)	30.6 (1.90)	3410 (1530)	NC
Bevacizumab (US) (group 2a)	21	4	0.25 (0.25-0.25)	30.0 (8.72)	31.3 (7.96)	1800 (2060)	NC

Multiple-dose IV toxicokinetic study in cynomolgus monkeys (Study ID 114831, GLP)

Twelve monkeys (6 females and 6 males) were assigned to 1 of 2 treatment groups (3/sex/group) receiving 50 mg/kg ABP 215 or 50 mg/kg bevacizumab (US) IV on days 1, 4, 8, 11, 15, 18, 22, and 25. Serum samples were collected from all animals for TK analysis at predose, 0.25, 1, 4, 8, 24, 48, and 72 hours post dose on day 1 and at predose, 0.25, 1, 4, 8, 24, 48, 72, and 96 hours post dose on day 25. Serum samples were analysed for ABP 215, bevacizumab (US) and anti-drug antibody (ADA) concentrations using validated ECL methods.

Results are presented in Figure 6 and Table 7. No sex differences in TK parameter estimates were observed. A moderate and similar accumulation in exposure was observed from day 1 to day 25 with an AR of 3.26 for ABP 215 and 3.40 for bevacizumab (US). Mean concentration-time profiles were similar between the 2 groups. Day 1 and day 25 serum TK parameters for ABP 215 were similar to those for the bevacizumab (US) dose group and contribute to the totality of evidence to support the demonstration of ABP 215 as a biosimilar product to bevacizumab.

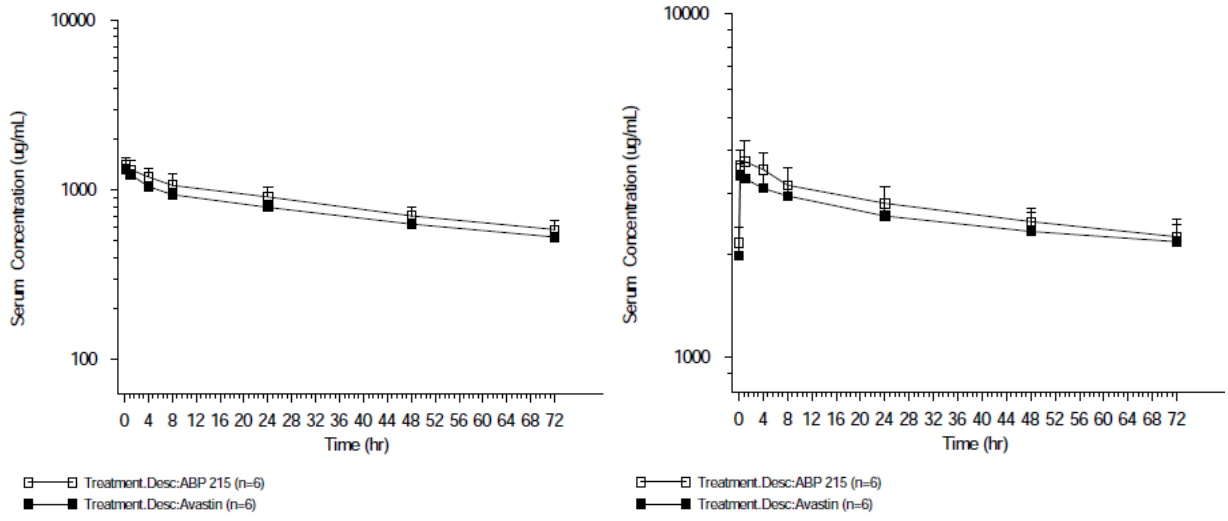


Figure 6: Serum concentration-time profiles (Semilog) on Day 1 (left panel) and Day 25 (right panel) in monkeys following IV administration of 50 mg/kg ABP 215 or bevacizumab (US)

Table 7: Toxicokinetic parameter values in cynomolgus monkeys after IV administration of ABP 215 or bevacizumab (US) twice weekly for 1 month

Route	Test Material	Day	N	t_{max} (hr)	C_{max} (ug/mL)	AUC_{0-72} (ug*hr/mL)	AR_{atio}
IV	ABP 215	1	6	0.25 (0.25-1.00)	1420 (138)	60400 (7950)	NC
		25	6	1.00 (0.25-1.00)	3750 (547)	196000 (20000)	3.26 (0.131)
	Avastin	1	6	0.25 (0.25-1.00)	1340 (49.7)	53500 (3870)	NC
		25	6	0.62 (0.25-1.00)	3400 (307)	182000 (22000)	3.40 (0.251)

Antibodies to ABP 215 or bevacizumab were not detected in any animals treated with ABP 215 or bevacizumab (US). However, considering that the immunoassay can tolerate up to 10 µg/mL of ABP 215 or bevacizumab at the lower limit of reliable detection, high levels of circulating drug could possibly have interfered with the ability to detect antibodies in the drug safety studies.

No distribution, biotransformation or excretion studies were conducted.

2.2.4. Toxicology

Single dose toxicity

No single-dose toxicity studies were conducted.

Repeat dose toxicity

Table 8: Overview of the toxicity study comparing ABP 215 and bevacizumab (US)

Study ID Species/strain GLP status	Test material Dose (route)	Number	Duration of dosing	Major findings
114831 Cynomolgus monkey GLP	ABP 215: 50 mg/kg/twice weekly (iv) Bevacizumab (US): 50 mg/kg/twice weekly (iv)	3/sex/group	4 weeks	Both substances: dark red area/foci at the intravenous injection sites of several animals in both groups. Light microscopic finding of subcutaneous haemorrhage commonly observed at iv injection sites. These changes were attributed to the injection procedure and not to the action of ABP 215 or bevacizumab (US).

ABP 215 and bevacizumab (US): 1-month intravenous toxicology study in the Cynomolgus monkey (study ID 114831, GLP)

The purpose of the study was to demonstrate a lack of unexpected effects with ABP 215 and to qualitatively compare the toxicity of ABP 215 and bevacizumab (US). Three monkeys/sex/group (initial age 2.6-3.4 years) were administered ABP 215 or bevacizumab (US) at 50 mg/kg IV twice weekly for 1 month (8 doses). A vehicle control group was not included because the study objective was to compare the 2 drug products; a vehicle control group was not considered necessary to identify the primary toxicity of femoral physeal dysplasia (the main and most sensitive endpoint of the study) and this study design reduced the use of nonhuman primates.

The dose selection of 50 mg/kg IV was based on the highest dose in the original 1-month toxicology study with bevacizumab (Avastin FDA Approval Package: Toxicology Data, 2004; Ryan et al, 1999), in which physeal dysplasia was observed in Cynomolgus monkeys. A 1-month study was considered to be of sufficient duration to identify potential differences in toxicological effects and to evaluate the most sensitive toxicity finding, physeal dysplasia. Samples were tested for TK parameters and anti-drug antibodies using validated ECL immunoassays (see section 4.1).

Mean TK parameters and concentration-time profiles were similar between the 2 groups (see Table 7: in section 4.2) and there were no apparent sex differences. No antidrug antibodies were detected in the ABP 215 or bevacizumab (US) groups; however, high levels of circulating drug may have interfered with the assay.

ABP 215 and bevacizumab (US) were well tolerated. No ABP 215- or bevacizumab (US)-related effects were observed on clinical signs, body weight, food consumption, physiologic measurements (heart rate and body temperature), ophthalmic or electrocardiogram examinations, haematology, serum chemistry, coagulation, urinalysis, or on macroscopic necropsy observations.

In the original bevacizumab 1-month toxicology study, a trend toward reduced organ to body weight of the uterus and ovaries that did not achieve statistical significance was described. In the current comparative study, ovarian and uterine to body weights were similar between the ABP 215 and bevacizumab (US) groups. Overall, average ovary-to-body weights were slightly reduced for ABP 215 and bevacizumab (US) compared to historical controls. Uterine weights were more variable, and one animal administered ABP 215 had a higher uterus weight than any of the historical controls; this animal was the only one to have histological evidence of having ovulated at least once, whereas the remainder of the animals in this study appeared histologically to be sexually immature or peripubertal.

In the original bevacizumab 1-month toxicology study, light microscopy histology revealed femoral physeal dysplasia, characterized by a linear cessation of growth line and chondrocyte hyperplasia, which was observed in all males at 50 mg/kg. In the current study, physeal dysplasia was observed in the femur of all animals dosed with either ABP 215 or bevacizumab (US), primarily characterized by a thicker than expected physeal growth plate that contained long columns of large chondrocytes. Femoral physeal dysplasia was mild in severity in both groups and affected all animals, indicating ABP 215 and bevacizumab (US) had similar effects.

Genotoxicity

No genotoxicity studies have been conducted.

Carcinogenicity

No carcinogenicity studies have been conducted.

Reproduction Toxicity

No reproductive and developmental toxicity studies have been conducted.

Toxicokinetic data

See “Absorption”

Local Tolerance

No dedicated local tolerance studies have been conducted.

Other toxicity studies

Immunogenicity of ABP 215 in comparison with bevacizumab (US) was assessed as part of the 1-month toxicology study in monkeys (Study 114831). No antidrug antibodies (ADA) were detected in the ABP 215 or bevacizumab (US) treated groups; however, high levels of circulating drug may have interfered with the assay.

2.2.5. Ecotoxicity / environmental risk assessment

Bevacizumab is a protein, which is expected to biodegrade in the environment and not be a significant risk to the environment. Thus, according to the “Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use” (EMEA/CHMP/SWP/4447/00), bevacizumab is exempt from preparation of an Environmental Risk Assessment as the product and excipients do not pose a significant risk to the environment.

2.2.6. Discussion on non-clinical aspects

A comprehensive number of *in vitro* functional assays has been conducted by the Applicant to substantiate similarity between ABP 215 and the European reference product Avastin (bevacizumab (EU)) in terms of Inhibition of proliferation of HUVEC cell, binding to VEGF-A_{121} and its isoforms, Inhibition of VEGF-A-mediated VEGFR-2 autophosphorylation .

The *in vitro* data have demonstrated similarity between ABP 215 and bevacizumab (EU). The similarity is further supported by *in vivo* PD studies from xenograft models comparing APB 215 and bevacizumab (US).

High-mannose may influence PK when present at relatively high levels. In general, the amount of high-mannose in ABP 215 (about 2.5%) is significantly higher than in bevacizumab (EU and US). In a cross-over study in rats, however, the PK properties of an early-developmental lot of ABP 215 with 3.5% high-mannose were comparable to bevacizumab (US).

A 4-week repeat-dose toxicity study was conducted with ABP 215 and bevacizumab (US) in cynomolgus monkeys, indicating comparable toxicity, toxicokinetic and immunogenic properties. Non-human primate toxicity studies are considered of limited value for biosimilarity evaluation and such studies are not generally recommended. The small format of these studies lacks any power to detect differences of potential clinical importance. It is, however, acknowledged that these studies were conducted as part of a global development.

The toxicokinetic properties of ABP 215 were characterized and compared with that of bevacizumab (US) in a GLP-compliant repeat-dose toxicity study in cynomolgus monkeys after single and multiple doses of 50 mg/kg/week (iv). The TK properties of ABP 215 were determined to be similar to that of bevacizumab (US).

Antibodies to bevacizumab (US) were not detected in any animal treated with ABP 215 or bevacizumab (US). However, high levels of circulating drug could possibly have interfered with the ability to detect antibodies in the drug safety studies.

No separate local tolerance studies have been conducted with ABP 215. The intended formulation for ABP 215 is identical to Avastin, and no new excipients are introduced. Consequently, evaluation of local tolerance is not required. Local tolerance endpoints were, however incorporated in the repeat-dose toxicity study, with similar findings in both treatment groups.

No anti-ABP 215 or anti-bevacizumab antibodies were detected in monkeys, however, high levels of circulating drug may have interfered with the assay. Although anti-drug antibody (ADA) -formation was not evaluated in rats, a decline in both ABP 215 and bevacizumab (US) PK profile was observed in a single-dose, crossover PK study in rats (study ID 114878), potentially related to ADA-formation.

Studies on secondary pharmacodynamics, safety pharmacology, pharmacodynamics drug interactions, genotoxicity, carcinogenicity, and reproduction and developmental toxicity were not conducted. This is considered acceptable for a biosimilar product, and is in accordance with EMA/CHMP/BMWP/403543/2010.

2.2.7. Conclusion on the non-clinical aspects

In view of the non-clinical data presented, ABP 215 can be considered similar to the reference product Avastin in terms of *in vitro* and *in vivo* functionality and toxicological, toxicokinetic and immunogenicity profiles.

The non-clinical information under section 5.3 of the Avastin SmPC applies also to the SmPC of MVASI.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study	Brief description	Number of subjects	Primary endpoints	Status
Phase I 20110216	Single-dose i.v. injection, three-arm, parallel group	202 (67/67/68 per arm)	AUC_{inf}, C_{max}	Completed
Phase III 20120265	A randomized, double-blind phase 3 study evaluating the efficacy and safety of ASP 215 compared with bevacizumab in subjects with advanced non-small cell lung cancer	630 (322/308 per arm)	Efficacy of ABP 215	Completed

2.3.2. Pharmacokinetics

In the phase I clinical study 20110216 in healthy subjects, the primary objective was to demonstrate bioequivalence of ABP 215 relative to EU-sourced, as well as US-sourced Avastin (bevacizumab) following a 3 mg/ kg body weight single iv injection. The secondary objective of this study was to determine the safety, tolerability, and immunogenicity of ABP 215 in healthy male subjects compared with bevacizumab (US) and bevacizumab (EU).

In the phase III clinical study 20120265 in patients, trough (pre-dose) plasma levels of bevacizumab or ABP 215 was determined following repeat dose administration at weeks 4, 7 and 13, and at end of study.

The same bioanalytical methods were used for the phase I study (20110216) and the phase III study (20120265). ABP 215, bevacizumab (EU) and bevacizumab (US) were determined by electrochemiluminescence (ECL) following an antibody capture procedure. Method validation and the results of incurred sample analysis have been provided.

Phase I study (20110216)

The study was conducted at two sites, one in EU and one in US. First enrolment was 13 June 2012, and the last end-of-study visit was 23 November 2012. Sample analyses were performed at ICON Development Solutions, LLC, Whitesboro, NY, USA between 24 September 2012 and 4 January 2013.

The original protocol dated 15 February 2012 was updated twice (19 March 2012 and 14 May 2012). The amendments involved corrections of typing errors, or otherwise minor changes. The most important changes were additions of exclusion criteria and minor changes to the clinical (adverse events) evaluation of subjects.

One amendment was made to the statistical analysis plan (SAP) 21 January 2013: AUC_{last} was added to the formal statistical analysis in the SAP – this parameter was not mentioned in the protocol. In the SAP amendment, the primary statistical analysis was also changed from being an analysis of protein content factor adjusted AUC_{last}, AUC_{inf}, and C_{max} to being an analysis of unadjusted AUC_{last}, AUC_{inf}, and C_{max}. The analysis of adjusted AUC_{last}, AUC_{inf}, and C_{max} was included as a sensitivity analysis. In the subgroup/ sensitivity analyses the unadjusted AUC_{last}, AUC_{inf}, and C_{max} was used as the parameters of interest.

This study was a randomised, single-blind, single-dose, 3-arm, parallel group, phase I study. A total of 202 healthy subjects (aged 18-45 years) were enrolled to the study; 34 + 34 subjects in the ABP 215 group and 67 in each of the bevacizumab (US and EU, respectively) groups. Sixty three (63), 64 and 64 subjects, respectively, completed the study. All 202 subjects were included in the safety population. In each group, all

subjects received a single dose (3 mg/ kg body weight) of ABP 215, EU-sourced bevacizumab, or US-sourced bevacizumab by i.v. infusion.

Test product was ABP 215 (batch number 1033020 (US) and 1032747 (EU)), which is representative for commercial batches of APB 215. Reference products were EU-sourced bevacizumab (batch H0135B13) and US-sourced bevacizumab (batch 970032).

Blood samples for PK analysis were collected at time zero (pre-dose), at 1.5 (end of infusion), 4, 8, 12 and 24 hours after the start of dosing, at days 3, 5, 8, 11, 15, 22, 29, 36, 43, 50, 64 and 78, and at the end of study visit (day 85).

The primary objective of the study was: To demonstrate bioequivalence as assessed principally by the area under the serum concentration-time curve (AUC) from time 0 extrapolated to infinity (AUC_{inf}) and the maximum observed serum concentration (C_{max}) of ABP 215 following a 3 mg/kg intravenous (IV) infusion relative to that from a 3 mg/kg IV infusion of bevacizumab (US) and bevacizumab (EU).

The secondary objective of this study was: To determine the safety, tolerability, and immunogenicity of ABP 215 in healthy male subjects compared with bevacizumab (US) and bevacizumab (EU).

Primary PK endpoints were:

- AUC_{inf} and C_{max} of ABP 215, bevacizumab (US), and bevacizumab (EU)
- AUC_{last} was included as primary PK endpoint after the clinical phase

Secondary Endpoints were:

- Subject incidence of treatment-emergent AEs (TEAEs), vital signs, laboratory safety tests, ECGs, and subject incidence of ADAs.
- Pharmacokinetic parameter AUC_{last} of ABP 215, bevacizumab (US), and bevacizumab (EU).

Equivalence of the primary endpoints (AUC_{inf}, C_{max}) was determined if the 90% CI for the ratio of geometric means of test-to-reference was within the predefined acceptance interval of 0.8 to 1.25.

Results

Serum concentration-time data for ABP 215, bevacizumab (US), and bevacizumab (EU) are summarised by treatment and time point in Figure 7 below.

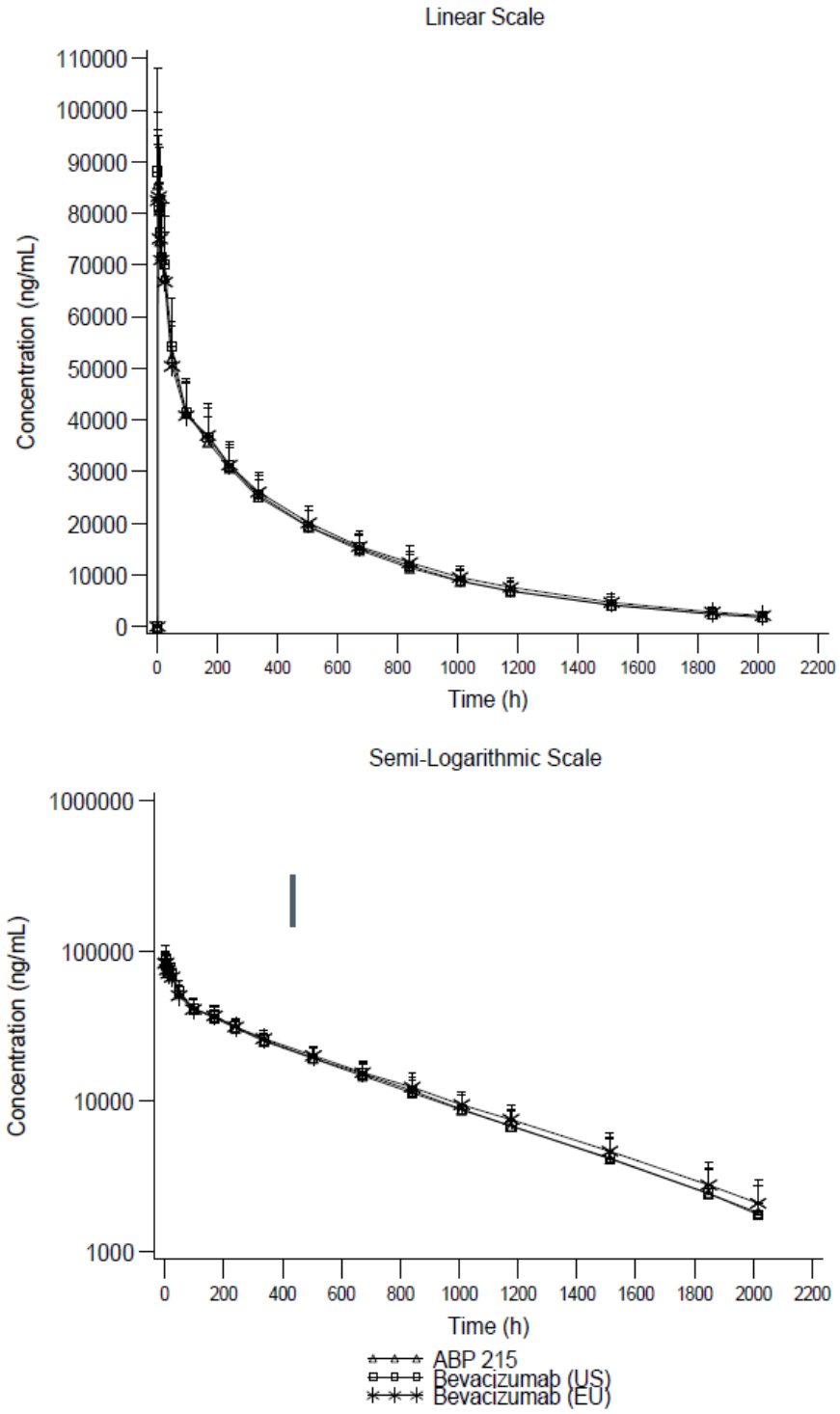


Figure 7: Mean (+SD) Serum ABP 215, Bevacizumab (US), and Bevacizumab (EU) Concentration-Time Profiles

Summary statistics of PK parameters

Summary of the Pharmacokinetic Parameters of ABP 215, Bevacizumab (US), and Bevacizumab (EU) and their Statistical Assessment is presented in Table 9 and Table 10 below.

Table 9: Summary of the Pharmacokinetic Parameters of ABP 215, Bevacizumab (US), and Bevacizumab (EU)

Treatment	C_{max} (µg/ml) GM [n] (GeoCV%)	AUC_{last} (µg•h/mL) GM [n] (GeoCV%)	AUC_{inf} (µg•h/mL) GM [n] (GeoCV%)	t_{max} (h) Median [n] (Min-Max)	$t_{½}$ (days) Mean [n] (SD)
ABP 215	87.2 [67] (14.4)	28200 [62] (14.9)	29400 [66] (16.6)	1.50 [67] (1.47-24.0)	17.7 [66] (3.68)
Bevacizumab (US)	89.1 [66] (19.7)	28500 [62] (14.9)	29600 [66] (16.4)	1.50 [66] (1.48-24.0)	17.5 [66] (3.39)
Bevacizumab (EU)	84.7 [64] (15.0)	29400 [64] (15.2)	30600 [66] (16.5)	3.94 [64] (1.47-8.00)	18.5 [66] (3.28)

Table 10: Summary of Statistical Assessment of ABP 215, Bevacizumab (US), and Bevacizumab (EU) Pharmacokinetic Parameters

Treatment and Comparison	C_{max} (µg/mL) Adjusted LS Geometric Mean [n]	AUC_{inf} (µg•h/mL) Adjusted LS Geometric Mean [n]	AUC_{last} (µg•h/mL) Adjusted LS Geometric Mean [n]
ABP 215	87.2 [67]	29400 [66]	28200 [62]
Bevacizumab (US)	89.1 [66]	29600 [66]	28500 [62]
Bevacizumab (EU)	84.7 [64]	30600 [66]	29400 [64]
	Ratio of Adjusted LS Geometric Means (90% CI)		
ABP 215 vs. Bevacizumab (US)	0.98 (0.933, 1.026)	0.99 (0.948, 1.042)	0.99 (0.946, 1.033)
ABP 215 vs. Bevacizumab (EU)	1.03 (0.982, 1.080)	0.96 (0.916, 1.006)	0.96 (0.920, 1.004)
Bevacizumab (US) vs. Bevacizumab (EU)	1.05 (1.004, 1.104)	0.97 (0.921, 1.012)	0.97 (0.930, 1.016)

Pharmacokinetic profiles for healthy volunteers were simulated using the population PK model for bevacizumab in patients with patient-specific covariates removed (Lu et al 2008). These simulations indicated a $t_{½}$ of 19.8 days, which was consistent with previous reports. Results from these simulations also predicted that PK monitoring for approximately 85 days would have resulted in greater than 97% of subject having AUC from time 0 to the last quantifiable concentration (AUC_{last}) values greater than 85% of AUC_{inf} (ie, the extrapolated AUC would have been ≤ 15 % of AUC_{inf}).

In accordance with the protocol, the following subgroup analyses were performed:

- Anti-drug Antibody: Not applicable, as no subjects tested positive for ADA

- Region: When comparing the results for ABP 215 and bevacizumab by region, the point estimates and 90 % CIs for the ratios of the 3 parameters were comparable to the overall analysis, and fully within 0.80 to 1.25:

Treatment and Comparison	C_{max} (µg/mL) Adjusted LS Geometric Mean [n]	AUC_{inf} (µg•h/mL) Adjusted LS Geometric Mean [n]	AUC_{last} (µg•h/mL) Adjusted LS Geometric Mean [n]
ABP 215 (US)	88.3	28700	27700
ABP 215 (EU)	86.1	30100	28800
Bevacizumab (US)	89.1 [66]	29600 [66]	28500 [62]
Bevacizumab (EU)	84.7 [64]	30600 [66]	29400 [64]
	Ratio of Adjusted LS Geometric Means (90% CI)		
ABP 215 (US) vs. Bevacizumab (US)	0.99 (0.936, 1.049)	0.97 (0.915, 1.027)	0.97 (0.918, 1.024)
ABP 215 (EU) vs. Bevacizumab (EU)	1.02 (0.959, 1.078)	0.98 (0.929, 1.042)	0.98 (0.929, 1.034)

- Body weight: Body weight was determined to be a significant predictor of bevacizumab PK. Following the inclusion of body weight as a covariate in the statistical model, bioequivalence between the three products was however confirmed.
- Outliers: Four samples were determined to be outliers and re-analysed due to an apparent systematic 10-fold error in these four samples, which were analysed at the same time by the same analyst. Re-analysis confirmed the assumption that a dilution error had occured in these four samples, and the re-assay result were included in the PK analysis.
- Protein Content Factor Adjusted Analysis: Protein contents were 25.6, 24.8, and 25.1 mg/mL for ABP 215, bevacizumab [US], and bevacizumab [EU], respectively. For all 3 parameters, the 90 % CIs for the ratios of adjusted GMs were fully within 0.80 to 1.25.

Phase III study (20120265)

Sample analyses were performed at ICON Development Solutions, LLC, Whitesboro, NY, USA.

This study was a randomised, double-blind, active-controlled study in adult subjects with non-squamous NSCLC receiving first-line chemotherapy with carboplatin and paclitaxel. A total of 630 patients were enrolled to the study; 322 subjects in the ABP 215 group and 308 in the bevacizumab group. 195 and 208 subjects, respectively, completed the study. In each group, all subjects received a dose of 15 mg/kg administered as an intravenous (IV) infusion every 3 weeks (Q3W) for 6 cycles.

Test product was ABP 215; Reference product was bevacizumab (Avastin EU).

Blood samples for PK analysis were collected at time zero (baseline), and at weeks 4, 7, 13 and 19. Anti-drug antibodies were determined at baseline, and at weeks 7, 13, 19 and at follow-up.

PK endpoint was C_{trough}.

The results are summarised in Table 11.

Table 11: Serum concentration by visit (Pharmacokinetic Analysis Population)

Visit [a] Statistic	ABP 215 (N = 322)	Bevacizumab (N = 308)
Baseline		
n	316	304
Mean (STD)	771.5 (6568.47)	2890.0 (25224.78)
Median	0.0	0.0
%CV	851.4	872.8
Min, Max	0, 74671	0, 303801
Week 4		
n	290	287
Mean (STD)	64322.3 (36474.39)	72336.5 (55009.29)
Median	60133.5	62530.0
%CV	56.7	76.0
Min, Max	0, 353536	0, 468204
Week 7		
n	277	275
Mean (STD)	99272.1 (57920.03)	105503.9 (67684.13)
Median	94054.0	96368.0
%CV	58.3	64.2
Min, Max	0, 457907	0, 569324
Week 13		
n	235	233
Mean (STD)	123348.3 (58762.68)	135544.7 (71264.03)
Median	124936.0	124421.0
%CV	47.6	52.6
Min, Max	0, 418854	10710, 488352
Week 19		
n	195	208
Mean (STD)	130986.7 (62427.68)	130636.8 (54429.11)
Median	131838.0	129018.5
%CV	47.7	41.7
Min, Max	308, 400105	1146, 296705

Baseline is defined as the last non-missing assessment taken prior to the first dose of study therapy.
Serum concentrations are reported in ng/mL. Records below the LLOQ are assigned a value of 0.
[a] This summary includes 7 predose samples that were found to have been collected post dose upon comparison of the dosing and PK collection dates and times.

2.3.3. Pharmacodynamics

No new pharmacodynamic data has been submitted as part of this application (see discussion on Clinical Pharmacology).

2.3.4. Immunogenicity

Serum samples for anti-drug antibodies were collected pre-dose on day 1 and on day 85 at the end of study visit. ADA positive cases were to be followed until ADA negative or for 1 year.

Analytical methods

A stepwise approach of screening, confirmatory and neutralising Ab assays was adopted.

Screening for Binding antibodies

Sera were screened for a signal-to-noise (S/N) value greater than the assay cut point and then tested in the specificity assay for signal inhibition in the presence of excess soluble drug before being regarded as positive for the presence of anti-ABP 215 antibodies, ADA. Direct evidence to support stability of the positive control Ab is not provided. The general principle of Ab stability is accepted and is supported by Hendricks et al 2014 for specific Abs to Adenovirus, Plasmodium sp. Circumzoite CS protein, HAV, and HBV including the 2nd international anti-HB standard as a positive polyclonal serum (NIBSC 07/164, 2008) – but affinity purified polyclonal rabbit Abs were not tested. Company reports were cited with details of the stability criteria for affinity purified anti-drug rabbit polyclonal Abs but no copies provided. In these specific circumstances this issue will not be pursued further.

Neutralising Ab assay

Very limited data have been provided to show that the assay is able to detect both ADA to ABP-215 and the RMP to an equivalent extent. Additional data are required to support the assumption, based on the cross-reactivity studies, that the ADA assays have equivalent sensitivity in detecting ADA to Avastin and ABP 215. Evidence of antigenic equivalence is presented, but evidence of antibody equivalence is lacking, although in this specific context the issue will not be pursued further. Drug tolerance indicates the screening, confirmatory and neutralising Ab assays should be able to detect ADA in the end of study samples when bevacizumab concentrations after a single dose are ~2 μg/ml. Typical trough bevacizumab levels of 100 – 150 μg/ml in the clinical studies should allow detection of higher titre ADA. The ADA assay may fail to detect binding ADA at trough bevacizumab levels of >250μg/ml seen in some patients although these subjects are likely to be immunosuppressed by the chemotherapy received. This problem might be avoided by analysis of end of study samples when bevacizumab levels should be lower.

Results

ADA subjects were to be listed and summarised by treatment group. Subgroup analysis of ADA subjects was planned but not executed as no ADA positive cases were identified.

2.3.5. Discussion on clinical pharmacology

The pharmacokinetic properties of ABP 215 were compared to those of both EU- and US-sourced bevacizumab (Avastin) in two clinical trials: A pivotal phase I clinical study in healthy subjects, following a 3 mg/ kg body weight single i.v. injection, and by analysis of trough (pre-dose) plasma levels of ABP 215 or bevacizumab following repeat dose administration in patients (15 mg/ kg).

The single dose parallel arm design with sampling over 4 serum half-lives is acceptable for PK determination.

The primary endpoints of the phase I clinical study (i.e. AUC_{last}, AUC_{inf} and C_{max}) with their 90% confidence intervals are well within the predefined acceptance range of 80-125%: The geometric LS means ratios for the comparison of ABP 215 and EU sourced Avastin for AUC_{last}, AUC_{inf} and C_{max} were 1.03, 0.96 and 0.96 and the corresponding 90%CIs [0.982-1.080], [0.916-1.006], [0.920-1.004], respectively.

Interpretation of the PK data is complicated by extreme values for t_{max} of 8 – 24 hours after a 90 minute infusion of ABP215 or Bevacizumab (EU) and median values for Bevacizumab (EU) were more than $2xt_{max}$ for ABP215 or Bevacizumab (US).

The T_{max} of ABP 215 occurred at 4 hours for 34.4% of subjects at the EU site versus 14.3% at the US site. The same trend of a higher proportion of subjects with tmax at 4 hours was observed for the bevacizumab (EU) group (48.4%) versus the bevacizumab (US) group (19.7%) In summary, the observed difference in median t_{max} for both ABP 215 and bevacizumab (EU) at the EU site is neither related to the product nor to infusion duration or PK sample collection deviations. The apparent difference between sites likely represents a chance occurrence that does not impact the ability to conclude PK similarity from this study.

It is noted that although bevacizumab-US vs bevacizumab-EU was not randomised between centres the allocation of ABP 215 (IMP) versus bevacizumab (RMP) was randomised at each centre.

The binding ADA validation indicated the impact of higher bevacizumab concentrations (>150 μg/ml) on the ability to detect ADA, The trough bevacizumab levels achieved, together with the PK data provided, indicate there is significant overlap with drug tolerance limits for the binding ADA assay before the end of study samples.

During the procedure, the applicant provided data regarding EOS sera tested for ADA by standard protocol from 95 of 102 subjects, (ABP 215 = 49, bevacizumab = 46) followed for approximately 6 months beyond end of treatment (EOT) period. One of 95 subjects tested was positive for binding ADA and negative for neutralizing ADA after EOT. This additional testing of 95 subjects at the EOS, when drug concentrations were low, provides reassurance of similar and low immunogenicity. The risk of false-negatives is mitigated by ADA assessment of all available post-EOT samples.

No difference in C_{trough} was observed between the ABP 215 and the bevacizumab groups at any time-point during the phase III clinical study.

No new pharmacodynamic data has been submitted as part of this application.

No validated PD markers considered relevant to predicting efficacy of bevacizumab in patients do so far exist. Therefore, no PD markers were included in the ABP 215 PK study, and clinical endpoints were utilised in the phase 3 study in NSCLC patients.

2.3.6. Conclusions on clinical pharmacology

The Applicant has demonstrated that the pharmacokinetic properties of ABP 215 are comparable to those of reference bevacizumab product following i.v. injection.

The clinical pharmacology information under section 5.2 of the Avastin SmPC applies also to Mvasi.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No dose response study was conducted.

2.4.2. Main study(ies)

Study 20120265: A randomized, double-blind, phase 3 study evaluating the efficacy and safety of ABP 215 compared with bevacizumab in subjects with advanced non-small cell lung cancer.

Methods

Clinical similarity was evaluated in subjects with advanced NSCLC under the conditions of use approved for bevacizumab.

The study was a randomised, double-blind, active-controlled study in adult subjects with non-squamous NSCLC receiving first-line chemotherapy with carboplatin and paclitaxel. Patients were to be randomised (1:1) to receive investigational product (ABP 215 or bevacizumab) at a dose of 15 mg/kg administered as an intravenous (IV) infusion every 3 weeks (Q3W) for 6 cycles. All subjects were to receive additional carboplatin and paclitaxel chemotherapy Q3W for at least 4 and not more than 6 cycles. Subjects were stratified by geographic region (Eastern Europe vs Western Europe vs Asia Pacific/Other vs North America), Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1), and sex. Maintenance monotherapy was not included in the study.

No reductions in IP dose were allowed in the study. If adverse events occurred that necessitated delaying IP, the dose remained unchanged once treatment resumed.

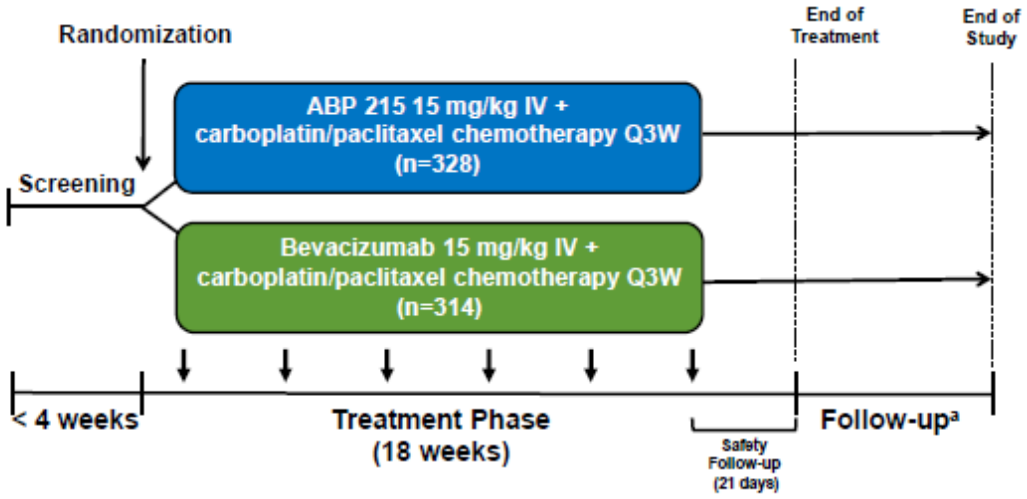
Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status; Type of Report/ Location
Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication (Module 5.3.5.1)								
Efficacy and Safety	20120265	Efficacy, safety, and immunogenicity of ABP 215 vs bevacizumab (EU)	Phase 3 randomized, double-blind, active-controlled study	ABP 215 vs bevacizumab (EU) 15 mg/kg IV infusion every 3 weeks	642 (328 ABP 215, 314 bevacizumab)	Stage IV/ recurrent non-squamous NSCLC; measurable disease per RECIST v1.1	19 wks	Complete; CSR/ Module 5.3.5.1 20120265

In the clinical study report (CSR) in the table: **Schedule of assessments and Procedures** the following was defined:

End of treatment was defined as 21 (+7) days after the last dose of investigational product or study-specified chemotherapy. A subject was to remain on the treatment phase until 21 days after the last dose of bevacizumab or study-specified chemotherapy.

Follow-up was defined as the period after the end of treatment visit were subjects were followed for disease progression and/or overall survival (OS) until the end of the clinical study, withdrawal of consent, lost to follow-up, death, or proscribed therapy (e.g. commercial bevacizumab, non-study anti-cancer treatment).

End of study was defined as the last day that protocol specified procedures were conducted for an individual subject.



IV = intravenous; Q3W = every 3 weeks
Investigational product (ABP 215 or bevacizumab) was administered in combination with carboplatin/paclitaxel for at least the first 4 treatments.
[a] Maintenance monotherapy not included.

Figure 8: Study scheme (Study 20120265)

Study Participants

The subject population was selected based upon the approved bevacizumab NSCLC indication and represents a sensitive population to rule out any clinically meaningful differences between ABP 215 and bevacizumab. Eligible subjects met the following key criteria:

1. Males and females ≥ 18 and < 80 years of age with histologically or cytologically confirmed non-squamous NSCLC

2. Stage 4 or recurrent metastatic NSCLC with measurable disease according to modified RECIST v1.1. For subjects with recurrent disease, at least 12 months had to have elapsed since completing adjuvant chemotherapy. Subjects had to have had a baseline scan (CT or MRI) of the chest and abdomen to assess disease burden before enrolling in study and receiving first-line chemotherapy for NSCLC. If the scan had been performed more than 28 days prior to randomization, an additional scan was to be obtained

3. Subjects had to be initiating first-line carboplatin/paclitaxel chemotherapy within 8 days after randomization and be expected to receive at least 4 cycles of chemotherapy

Treatments

Subjects were randomly assigned to one of the following two treatment arms:

- Treatment A: ABP 215, IV infusion, 15 mg/kg Q3W with IV carboplatin (area under the concentration-time curve [AUC] of 6) and paclitaxel (200 mg/m2).
- Treatment B: bevacizumab, IV infusion, 15 mg/kg Q3W with IV carboplatin (AUC 6) and paclitaxel (200 mg/m2).

In both treatment arms, doses were administered Q3W (±7 days) for 6 cycles. The dosage for both ABP 215 and bevacizumab was 15 mg/kg Q3W. The dosage was chosen to align with the EU-approved dosing instructions for the treatment of NSCLC with bevacizumab in combination with carboplatin and paclitaxel.

All of the following were prohibited at any time during the study:

- any non-study anti-cancer treatment
- commercial bevacizumab
- any experimental (biological or non-biological) therapy (within or outside a clinical study)

In the SmPC for Avastin, monotherapy is recommended for NSCLC patients after combination treatment until disease progression or unwanted toxicity. Maintenance monotherapy post-treatment was not included.

After the treatment phase, subjects then entered a follow-up period during which they were followed for disease progression and overall survival until one of the following:

- consent was withdrawn, they were lost to follow-up, died, or had proscribed therapy (eg. commercial bevacizumab, non-study anticancer treatment), thus marking the end of study for that subject, or
- the end of the clinical study, defined as the last subject's completion of the treatment phase.

Objectives

The primary objective for this study was to compare the efficacy of ABP 215 with bevacizumab. The secondary objective was to assess the safety and immunogenicity of ABP 215 compared with bevacizumab, which are in accordance with the biosimilar approach. However, although not stated explicitly in the study objective, it is assumed, based on the statistical methodology, that the primary objective of the trial was to demonstrate biosimilarity between ABP 215 and bevacizumab.

Outcomes/endpoints

Efficacy:

The primary efficacy endpoint was the risk ratio (RR) of objective response rate (ORR), according to RECIST version 1.1, as assessed by the central, independent, blinded radiologist. The primary analysis of ORR was based on the ITT population, using data from the central, independent, blinded radiologists' review. The pre-specified equivalence margin for the primary endpoint (RR of ORR) was 0.67 to 1.5.

The secondary efficacy endpoints were the RD of ORR, duration of response (DOR), and progression-free survival (PFS).

Safety:

The safety variables evaluated were incidence of adverse events, OS, changes in clinical laboratory tests and vital signs, and incidence of anti-drug antibodies (ADAs).

Sample size

Approximately 620 subjects overall (310 subjects per arm) were to be randomized. The sample size was chosen to achieve 95% power to demonstrate equivalence between ABP 215 and bevacizumab on the primary efficacy endpoint (risk ratio of ORR) with a margin of (0.67, 1.5) at a 2-sided significance level of 0.05. It was assumed that the ORR would be approximately 38% (Botrel et al, 2011) in both the ABP 215 and bevacizumab arms.

Randomisation

Blinding (masking)

Statistical methods

This was a comparative study designed to demonstrate clinical equivalence of ABP 215 and bevacizumab in adult subjects with NSCLC receiving first-line chemotherapy with carboplatin and paclitaxel. The study was designed to inferentially assess similarity between ABP 215 and bevacizumab with regard to ORR and to descriptively assess other endpoints.

The primary study hypothesis was that there was no clinically meaningful difference between ABP 215 and bevacizumab for ORR. The hypothesis was tested by comparing the 2-sided 90% confidence interval (CI) of the risk ratio in ORR between ABP 215 and bevacizumab with an equivalence margin of (0.67, 1.5). A generalised linear model adjusted for the stratification factors was fitted using the SAS® procedure "GENMOD".

To assess the robustness of the primary ORR analysis results, the primary analysis was repeated using data from the central, independent, blinded radiologists' review in the PP population and in the tumour response set.

A sensitivity analysis was also performed including the following baseline covariates in the model, in addition to the randomization stratification factors: weight loss in the last 6 months, age group, stage IV/recurrent disease at baseline, race, smoking history, EGFR mutation status, and ALK status.

The risk ratio for ORR was also examined in the subgroups as defined by baseline covariates (including geographic region, ECOG performance status, gender, etc…).

The risk difference for ORR was calculated using a method analogous to that used for the risk ratio. The RD was summarised with 90% and 95% CIs for all of the analyses done for the risk ratio. A forest plot was created to summarize the variability in the RDs using 95% CIs across the subgroups.

The non-inferiority margin of 12.5% was chosen based on a meta-analysis consisting of the 4 published, randomized bevacizumab studies in NSCLC cited in Botrel et al, 2011, and was chosen to be less than the

lower bound of 95% CI for the risk difference of ORR, which is the smallest effect size that bevacizumab would be reliably expected to have compared with placebo.

Results

Participant flow

Protocol amendments

The original protocol (Protocol Version 1.0) was issued on 1 March 2013. There were two protocol amendments. No subjects were enrolled under Protocol Version 1.0. Amendment 1 (Protocol Version 2.0) was issued on 22 April 2013. Amendment 2 (Protocol Version 3.0) was issued on 24 March 2014.

Recruitment

The phase 3 study was conducted at 101 sites (14 sites in the US, 11 in Russia, 10 in Australia, nine in Germany, eight in Poland, seven in Hungary, seven in Romania, six in Italy, six in Spain, five in Bulgaria, five in Greece, three in the Czech Republic, three in Mexico, three in Taiwan, two in the Netherlands, one in Canada, and one in Hong Kong). Russia, Taiwan and Hong Kong are countries outside the EU and the OECD mutual acceptance of data agreement.

The first subject in study 20120265 was enrolled the 11th of November 2013, and last subject completed study the 23rd of July 2015.

Conduct of the study

A total of 642 subjects was included in the ITT analysis set (328 and 314 subjects were randomised to ABP 215 and bevacizumab, respectively.

One hundred two subjects (102; 15.9% randomised subjects; 58 [17.7%] and 44 [14.0%]) completed the study (i.e., were ongoing in active follow-up when the study was terminated). Reasons for ending the clinical study included death (related to adverse events or disease progression), protocol violations, lost to follow-up, physician decision, withdrawal of consent, plan to receive commercial bevacizumab or non-study anticancer therapy, decision by sponsor, or other.

Baseline data

Table 12: Baseline Disease Characteristics (Intent-to-treat Population)

Variable	ABP 215 (N = 328)	Bevacizumab (N = 314)	Total (N = 642)
ECOG performance status [n (%)]			
Grade 0	127 (38.7)	117 (37.3)	244 (38.0)
Grade 1	201 (61.3)	197 (62.7)	398 (62.0)
Staging of original diagnosis [n (%)]			
Occult (hidden stage)	1 (0.3)	0 (0.0)	1 (0.2)
Stage 0 (carcinoma in situ)	0 (0.0)	0 (0.0)	0 (0.0)
Stage I	7 (2.1)	13 (4.1)	20 (3.1)
Stage II	9 (2.7)	3 (1.0)	12 (1.9)
Stage IIIA	6 (1.8)	9 (2.9)	15 (2.3)
Stage IIIB	2 (0.6)	7 (2.2)	9 (1.4)
Stage IV	303 (92.4)	281 (89.5)	584 (91.0)
Missing	0 (0.0)	1 (0.3)	1 (0.2)
Tumor classification at screening [n (%)]			
T0	9 (2.7)	14 (4.5)	23 (3.6)
T1a	21 (6.4)	20 (6.4)	41 (6.4)
T1b	18 (5.5)	17 (5.4)	35 (5.5)
T2a	69 (21.0)	69 (22.0)	138 (21.5)
T2b	34 (10.4)	29 (9.2)	63 (9.8)
T3	75 (22.9)	74 (23.6)	149 (23.2)
T4	100 (30.5)	91 (29.0)	191 (29.8)
Missing	2 (0.6)	0 (0.0)	2 (0.3)
Metastasis classification at screening [n (%)]			
M1a	120 (36.6)	122 (38.9)	242 (37.7)
M1b	206 (62.8)	191 (60.8)	397 (61.8)
Missing	2 (0.6)	1 (0.3)	3 (0.5)
Nodes classification at screening [n (%)]			
N0	63 (19.2)	68 (21.7)	131 (20.4)
N1	30 (9.1)	20 (6.4)	50 (7.8)
N2	128 (39.0)	120 (38.2)	248 (38.6)
N3	104 (31.7)	106 (33.8)	210 (32.7)
Missing	3 (0.9)	0 (0.0)	3 (0.5)

Variable	ABP 215 (N = 328)	Bevacizumab (N = 314)	Total (N = 642)
Time since original diagnosis (weeks)			
n	328	314	642
Mean (STD)	13.4 (34.18)	16.8 (57.84)	15.1 (47.25)
Median	4.0	4.0	4.0
Q1, Q3	2.0, 7.0	2.0, 7.0	2.0, 7.0
Min, Max	1, 251	1, 762	1, 762
Geographic region [n (%)]			
Eastern Europe	189 (57.6)	186 (59.2)	375 (58.4)
Western Europe	78 (23.8)	76 (24.2)	154 (24.0)
North America	31 (9.5)	26 (8.3)	57 (8.9)
Asia Pacific/Other	30 (9.1)	26 (8.3)	56 (8.7)
Weight loss in last 6 months [n (%)]			
0 - 5%	289 (88.1)	276 (87.9)	565 (88.0)
> 5 - 10%	39 (11.9)	37 (11.8)	76 (11.8)
Missing	0 (0.0)	1 (0.3)	1 (0.2)
Stage IV/recurrent disease at baseline [n (%)]			
Stage IV	309 (94.2)	290 (92.4)	599 (93.3)
Recurrent disease	19 (5.8)	24 (7.6)	43 (6.7)
Smoking status [n (%)]			
Never	65 (19.8)	76 (24.2)	141 (22.0)
Former	163 (49.7)	158 (50.3)	321 (50.0)
Current	100 (30.5)	80 (25.5)	180 (28.0)
EGFR expression status [n (%)]			
Positive	6 (1.8)	2 (0.6)	8 (1.2)
Negative	79 (24.1)	78 (24.8)	157 (24.5)
Unknown	57 (17.4)	55 (17.5)	112 (17.4)
Not performed	186 (56.7)	179 (57.0)	365 (56.9)
EGFR mutation status [n (%)]			
Positive	7 (2.1)	8 (2.5)	15 (2.3)
Negative	130 (39.6)	130 (41.4)	260 (40.5)
Unknown	8 (2.4)	1 (0.3)	9 (1.4)
Not performed	183 (55.8)	175 (55.7)	358 (55.8)

ALK status [n (%)]			
Positive	4 (1.2)	4 (1.3)	8 (1.2)
Negative	80 (24.4)	71 (22.6)	151 (23.5)
Not done	244 (74.4)	239 (76.1)	483 (75.2)

ALK = anaplastic lymphoma receptor tyrosine kinase; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; max = maximum; min = minimum; Q1 = 25th percentile; Q3 = 75th percentile STD = standard deviation.
Not performed/not done = EGFR/ALK status not assessed.

Patients with NSCLC expressing activating mutations in EGFRs or ALK translocations were included in the phase 3 study; receptor status assessment was not required at baseline. Recent clinical development of targeted drugs, e.g. monoclonal antibodies and tyrosine kinase inhibitors (TKIs), has dramatically changed cancer treatment, including treatment of NSCLC. Several TKIs have been approved for first line therapy of patients with metastatic NSCLC with activating mutations in EGFR and ALK, and are now standard therapy for this condition in Europe and other western countries. These patients are known to do less well with up front chemotherapy. Ideally, to reduce unbalanced arms and thereby uncertainty in the data, all patients should have been tested for EGFR and ALK mutations before entering the study; and patients positive for either of the mutation/rearrangement should have been be excluded. In addition, to avoid unbalanced enrolment of mutation-negative and mutation-unknown patients, the randomisation of patients harbouring either of these mutations should have been stratified. Therapies targeting the EGF-receptor mutations, were approved for first line use in metastatic NSCLC patients already in 2011. However, given that the advice from CHMP in 2011 did not discuss this subject; the use of an adequate randomisation procedure when enrolling patients; and in addition, results are indicating similarity between the two products, the chosen strategy are considered acceptable.

Numbers analysed

All the randomised subjects were included in the ITT population. Of the randomised subjects, 633 subjects (98.6%; 324 [98.8%] and 309 subjects [98.4%] on ABP 215 and bevacizumab reference, respectively) received at least one dose of bevacizumab and were included in the safety analysis set.

The PP population constituted approximately 86% of the ITT population.

Table 13: Subject Populations (All Subjects)

Population Reason for Exclusion	ABP 215	Bevacizumab	Total
Subjects screened			820[a]
Subjects randomized (ITT population) [n]	328	314	642
Safety analysis set[b] [n (%)]	324 (98.8)	309 (98.4)	633 (98.6)
Did not receive IP [n (%)]	4 (1.2)	5 (1.6)	9 (1.4)
Tumor response set[c] [n (%)]	317 (96.6)	305 (97.1)	622 (96.9)
Did not receive IP [n (%)]	4 (1.2)	5 (1.6)	9 (1.4)
No measurable disease at screening [n (%)]	7 (2.1)	4 (1.3)	11 (1.7)
PP population[d] [n (%)]	281 (85.7)	274 (87.3)	555 (86.4)
Did not receive IP [n (%)]	4 (1.2)	5 (1.6)	9 (1.4)
Did not have measurable disease at screening [n (%)]	7 (2.1)	4 (1.3)	11 (1.7)
Did not complete 6 cycles of IP due to reasons other than disease progression, death, or adverse event [n (%)]	41 (12.5)	34 (10.8)	75 (11.7)
Did not complete at least 4 cycles of chemotherapy due to reasons other than disease progression, death, or adverse event [n (%)]	25 (7.6)	23 (7.3)	48 (7.5)
Protocol deviation affecting evaluation for primary objective [n (%)]	5 (1.5)	3 (1.0)	8 (1.2)
Pharmacokinetics population[e] [n (%)]	322 (98.2)	308 (98.1)	630 (98.1)
Did not receive IP [n (%)]	4 (1.2)	5 (1.6)	9 (1.4)
Did not have evaluable serum concentration [n (%)]	5 (1.5)	6 (1.9)	11 (1.7)

ITT = intent-to-treat; IP = investigational product; PP = per-protocol.
Note: % = Percent of all randomized subjects.

a. Three additional subjects were screened but were not entered into the IXRS database. These subjects signed informed consent forms but did not undergo any other study-specific procedures
b. Safety analysis set: All subjects who received any amount of IP. Subjects are summarized according to their actual treatment received.
c. Tumour response set: All subjects who were randomised, treated, and with measurable disease at screening as determined by the central radiologist. Subjects are summarised according to their actual treatment received.
d. PP population: Subset of the tumour response set who completed the treatment period (6 cycles of IP and at least 4 cycles of chemotherapy) or who discontinued IP or chemotherapy prior to completing 6 cycles of IP and at least 4 cycles of chemotherapy due to reasons allowed per protocol (i.e. disease progression, adverse events and death), and did not experience a protocol deviation that affected their evaluation for the primary objective of the study. Subjects are summarised according to their actual treatment received.
e. Pharmacokinetics population: The subset of subjects in the safety analysis set that provide at least one serum concentration of ABP 215 or bevacizumab.

The mean (STD) actual follow-up time from randomisation was 4.7 (3.04) and 5.0 (3.17) months for ABP 215 and bevacizumab, respectively (**Error! Reference source not found.**).

Table 14: Subject Study Disposition (ITT Population)- Follow-up

Variable	ABP 215 (N = 328) n (%)	Bevacizumab (N = 314) n (%)	Total (N = 642) n (%)
Actual follow-up time (months)[d]			
n	328	314	642
Mean (std)	4.7 (3.04)	5.0 (3.17)	4.9 (3.10)
Median	4.0	4.0	4.0
Q1, Q3	3.0, 6.0	3.0, 7.0	3.0, 6.0
Min, Max	0, 16	0, 17	0, 17

a Percentage is calculated as n/N1*100.
b Percentage is calculated as n/N2*100.
c Percentage is calculated as n/N3*100.
d A subject's actual follow-up time is defined as time from the randomisation date to the last on-study follow-up visit.

Outcomes and estimation

Primary endpoint:

The primary efficacy variable was the RR of ORR, and the pre-specified equivalence margin was (0.67, 1.5). ORR was defined as the incidence rate of either complete response (CR) or partial response (PR) using RECIST v1.1.

Table 15: Summary of Objective Response Rate – Primary Efficacy (ITT)

	ABP 215 (N = 328)	Bevacizumab (N = 314)	Total (N = 642)
Best overall response [n (%)]			
Complete response (CR)	2 (0.6)	2 (0.6)	4 (0.6)
Partial response (PR)	126 (38.4)	129 (41.1)	255 (39.7)
Stable disease (SD)	144 (43.9)	137 (43.6)	281 (43.8)
Progressive disease (PD)	21 (6.4)	18 (5.7)	39 (6.1)
Not evaluable (NE)	35 (10.7)	28 (8.9)	63 (9.8)
Objective response rate (ORR)[a] [n (%)]			
Yes	128 (39.0)	131 (41.7)	259 (40.3)
No	200 (61.0)	183 (58.3)	383 (59.7)
Risk ratio (ABP 215/Bevacizumab)[b]	0.93		
90% CI for risk ratio[b]	(0.80, 1.09)		
95% CI for risk ratio[b]	(0.77, 1.12)		
Risk difference (ABP 215 - Bevacizumab) (%)[b]	-2.90		
90% CI for risk difference (%)[b]	(-9.26, 3.45)		
95% CI for risk difference (%)[b]	(-10.48, 4.67)		

CI = confidence interval
Note: For the primary efficacy analysis, objective response is determined by central, independent, blinded radiologists. Subjects without any post baseline tumour assessment are included in the NE category per RECIST 1.1.

a. Objective response rate is defined as the percentage of subjects with an objective response.

Objective response is defined as a best overall response of PR or CR as defined by RECIST v1.1.

b. Point estimate and CI are estimated using a generalised linear model adjusted for the randomisation stratification factors geographic region, ECOG performance status, and sex.

Similarity between ABP 215 and EU-licensed bevacizumab reference product was demonstrated within the pre-specified equivalence margins (0.67, 1.5; 12.5 %).

Secondary endpoints:

Risk difference for objective response rate

Risk difference based on the central, independent, blinded radiologists' review in the ITT population indicated that the 2 treatment arms were similar in the ITT population (RD = -2.90%; 90% CI: -9.26% to 3.45%; 95% CI: -10.48% to 4.67%), in the PP population (RD = -2.82%; 90% CI: -9.73% to 4.10%; 95% CI: -11.06% to 5.42%), in the tumour response set (RD = -2.78%; 90% CI: -9.27% to 3.71%; 95% CI: -10.51% to 4.95%), in the ITT population when using the investigator's assessment of response (RD = -0.68%; 90% CI: -7.11% to 5.76%; 95% CI: -8.34% to 6.99%), and in the model with additional covariates, using the ITT population and the central response (RD = -3.24%; 90% CI: -9.54% to 3.05%; 95% CI: -10.74% to 4.26%).

Table 16: Summary of Objective Response Rate (ORR) - Sensitivity Analysis (Per Protocol Population)

	ABP 215 (N = 281)	Bevacizumab (N = 274)	Total (N = 555)
Best overall response [n (%)]			
Complete response (CR)	2 (0.7)	2 (0.7)	4 (0.7)
Partial response (PR)	119 (42.3)	123 (44.9)	242 (43.6)
Stable disease (SD)	123 (43.8)	120 (43.8)	243 (43.8)
Progressive disease (PD)	19 (6.8)	18 (6.6)	37 (6.7)
Not evaluable (NE)	18 (6.4)	11 (4.0)	29 (5.2)
Objective response rate (ORR)[a] [n (%)]			
Yes	121 (43.1)	125 (45.6)	246 (44.3)
No	160 (56.9)	149 (54.4)	309 (55.7)
Risk ratio (ABP 215/Bevacizumab)[b]	0.94		
90% CI for risk ratio[b]	(0.80, 1.10)		
95% CI for risk ratio[b]	(0.78, 1.13)		
Risk difference (ABP 215 - Bevacizumab) (%)[b]	-2.82		
90% CI for risk difference (%)[b]	(-9.73, 4.10)		
95% CI for risk difference (%)[b]	(-11.06, 5.42)		

Note: For the sensitivity analysis using the per protocol population, objective response is determined by an independent, blinded radiologist. Subjects without any post-baseline tumour assessment are included in the NE category per RECIST 1.1.
[a] Objective response rate is defined as the percentage of subjects with an objective response. Objective response is defined as a best overall response of partial response or complete response as defined by RECIST v 1.1.
[b] Point estimate and confidence interval are estimated using a generalized linear model adjusted for the randomisation stratification factors geographic region, ECOG performance status, and sex.

The applicant presented results of the risk difference (RD) of ORR from the clinical phase 3 study in NSCLC patients in both the ITT and PP population with 95% CI at week 19, as well as at week seven and 13, which confirmed similarity between ABP 125 and reference bevacizumab.

Table 17: Time to First Objective Response Based on Central Assessment (Intent-to-treat Population)

	ABP 215 (N = 281)	Bevacizumab (N = 274)	Risk Difference of ORR[a, b]	
			Point Estimate[c]	95% CI[c]
Cumulative assessment of first objective response[d] [n (%)]				
[0, 7] weeks	61 (18.6)	51 (16.2)	1.40	-4.49, 7.28
[0, 13] weeks	99 (30.2)	102 (32.5)	-2.71	-9.83, 4.42
[0, 19] weeks	121 (36.9)	123 (39.2)	-2.56	-10.05, 4.93
During study	128 (39.0)	131 (41.7)	-2.90	-10.48, 4.67

CI = confidence interval; ORR = objective response rate; RECIST = Response Evaluation Criteria in Solid Tumors
Note: Objective response (ie, partial response or complete response) is determined by an independent, blinded radiologist using RECIST v1.1. Subject's first objective response may not necessarily be the subject's best overall response.
[a] Objective response rate is defined as the percentage of subjects with a best overall response of partial response or complete response per RECIST v1.1.
[b] Risk difference of ORR is defined as the ORR in the ABP 215 arm minus the ORR in the bevacizumab arm.
[c] Point estimate and CI are estimated using a generalized linear model adjusted for the randomization stratification factors geographic region, Eastern Cooperative Oncology Group performance status, and sex.
[d] Percentages are based on column totals.

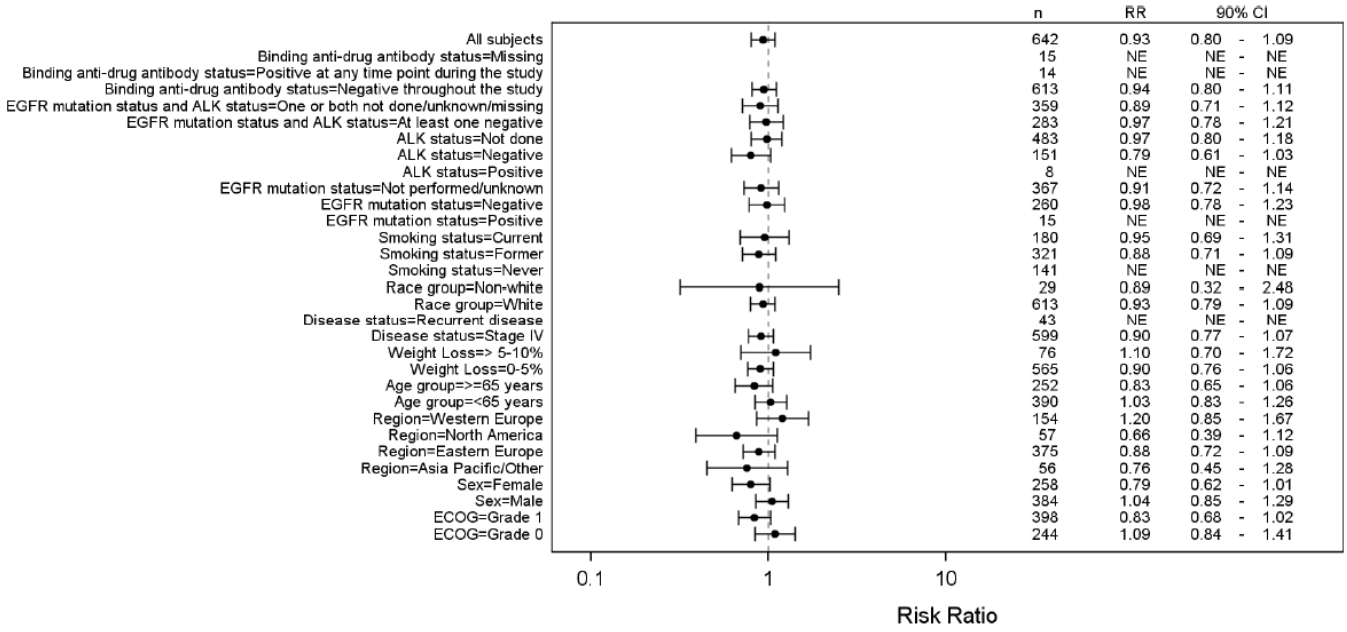
Table 18: Time to First Objective Response Based on Central Assessment (Per Protocol Population)

	ABP 215 (N = 281)	Bevacizumab (N = 274)	Risk Difference of ORR[a, b]	
			Point Estimate[c]	95% CI[c]
Cumulative assessment of first objective response[d] [n (%)]				
[0, 7] weeks	60 (21.4)	48 (17.5)	2.68	-3.88, 9.24
[0, 13] weeks	93 (33.1)	96 (35.0)	-2.67	-10.49, 5.16
[0, 19] weeks	114 (40.6)	117 (42.7)	-2.49	-10.67, 5.68
During study	121 (43.1)	125 (45.6)	-2.82	-11.06, 5.42

CI = confidence interval; ORR = objective response rate; RECIST = Response Evaluation Criteria in Solid Tumors
Note: Objective response (ie, partial response or complete response) is determined by an independent, blinded radiologist using RECIST v1.1. Subject's first objective response may not necessarily be the subject's best overall response.
[a] Objective response rate is defined as the percentage of subjects with a best overall response of partial response or complete response per RECIST v1.1.
[b] Risk difference of ORR is defined as the ORR in the ABP 215 arm minus the ORR in the bevacizumab arm.
[c] Point estimate and CI are estimated using a generalized linear model adjusted for the randomization stratification factors geographic region, Eastern Cooperative Oncology Group performance status, and sex.
[d] Percentages are based on column totals.

- **Examination of Subgroups**

The risk ratio for ORR was also examined in the subgroups as defined by the stratification covariates geographic region (Eastern Europe vs Western Europe vs Asia Pacific/Other vs North America), ECOG performance status (0 vs 1), sex (men vs women) and a number of additional covariates: weight loss in the last 6 months, age group, stage IV/recurrent disease at baseline, race, smoking history, EGFR mutation status, and ALK status and ADA status.



ALK = anaplastic lymphoma receptor tyrosine kinase; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor.
Point estimate and 90% confidence interval of the risk ratio (ABP215/Bevacizumab) are estimated using a generalised linear model adjusted for the randomisation stratification factors geographic region, ECOG performance status, and sex. For subgroup analyses for each of the randomization stratification factors, the 2 remaining factors were adjusted for in the model. Two subjects who selected both White and Non-white races are included in the Non-white category for subgroup analyses.

Figure 9: Forest Plot of Risk Ratio of ORR by Subgroup (Intent-to-treat Population)

There are some considerable discrepancies in RR of ORR between the gender subgroups (Female RR of 0.79, 90%CI: 0.62 to 1.01; Male RR of 1.04, 90%CI: 0.85 to 1.29) and between the ECOG subgroups (Grade 1 RR of 0.83, 90%CI: 0.68 to 1.02; Grade 2 RR of 1.09, 90%CI: 0.84 to 1.41).

The applicant provided ORR per treatment arm separately for women and men, and separately for ECOG PS.

Table 19: Summary of Objective Response Rate by Sex (Intent-to-treat Population)

	Male		Female	
	ABP 215 (N = 196) n (%)	Bevacizumab (N = 188) n (%)	ABP 215 (N = 132) n (%)	Bevacizumab (N = 126) n (%)
ORR[a] [n (%)]				
Yes	79 (40.3)	73 (38.8)	49 (37.1)	58 (46.0)
No	117 (59.7)	115 (61.2)	83 (62.9)	68 (54.0)
Risk ratio (ABP 215/ Bevacizumab)[b]	1.04		0.79	
90% CI for risk ratio	(0.85, 1.29)		(0.62, 1.01)	
95% CI for risk ratio	(0.81, 1.34)		(0.59, 1.06)	

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ORR = objective response rate
Note: For the primary efficacy analysis, objective response was determined by independent central, blinded radiologists. Subjects without any postbaseline tumor assessment were included in the not-evaluable category per RECIST version 1.1.
[a] Objective response rate is defined as the percentage of subjects with an objective response. Objective response is defined as the best overall response of partial response or complete response as defined by RECIST version 1.1.
[b] Point estimate and CI are estimated using a generalized linear model adjusted for the randomization stratification factors geographic region and ECOG performance status.

Table 20: Summary of Objective Response Rate by ECOG Performance Status (Intent-to-treat Population)

	ECOG Performance Status 0		ECOG Performance Status 1	
	ABP 215 (N = 127) n (%)	Bevacizumab (N = 117) n (%)	ABP 215 (N = 201) n (%)	Bevacizumab (N = 197) n (%)
ORR[a] [n (%)]				
Yes	56 (44.1)	46 (39.3)	72 (35.8)	85 (43.1)
No	71 (55.9)	71 (60.7)	129 (64.2)	112 (56.9)
Risk ratio (ABP 215/ Bevacizumab)[b]	1.09		0.83	
90% CI for risk ratio	(0.84, 1.41)		(0.68, 1.02)	
95% CI for risk ratio	(0.80, 1.49)		(0.65, 1.06)	

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ORR = objective response rate
Note: For the primary efficacy analysis, objective response was determined by independent central, blinded radiologists. Subjects without any postbaseline tumor assessment were included in the not-evaluable category per RECIST version 1.1.
[a] Objective response rate is defined as the percentage of subjects with an objective response. Objective response is defined as the best overall response of partial response or complete response as defined by RECIST version 1.1.
[b] Point estimate and CI are estimated using a generalized linear model adjusted for the randomization stratification factors geographic region and sex.

The Applicant were requested to comment on these discrepancies, as well as to present ORR per treatment arm separately for women and men, and separately for ECOG subgroups. In their response, the Applicant provided ORR per treatment arm separately for women and men, and separately for ECOG PS. This issue is considered resolved.

Ancillary analyses

N/A

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 21: Summary of Efficacy for Study 20120265

Title: A randomised, double-blind, phase 3 study evaluating the efficacy and safety of ABP 215 compared with bevacizumab in subjects with advanced non-small cell lung cancer.		
Study identifier	20120265	
Design	Randomised, double-blind, active-controlled, two-arm study	
	Duration of main phase:	19 weeks of treatment and follow-up for disease progression and overall survival until the end of the clinical study, consent was withdrawn, lost to follow-up, died, or had proscribed therapy.
Hypothesis	Equivalence	
Treatments groups	ABP 215	• BP 215 15 mg/kg intravenous (IV) infusion Q3W for 6 cycles • hemotherapy: Carboplatin (AUC 6) + Paclitaxel 200 mg/m^2 Q3W for at least 4 and not more than 6 cycles 328 subjects randomized
	Bevacizumab	• bevacizumab 15 mg/kg intravenous (IV) infusion Q3W for 6 cycles • hemotherapy: Carboplatin (AUC 6) + Paclitaxel 200 mg/m2 Q3W for at least 4 and not more than 6 cycles 314 subjects randomized

Endpoints and definitions	Primary endpoint	Risk ratio of objective response rate (ORR) per RECIST v1.1	ORR is defined as the percentage of subjects with a best overall response of complete response (CR) or partial response (PR) during study, based on independent, blinded, central radiologists review. Risk ratio (ABP 215/Bevacizumab) of ORR is defined as the ratio of ORR in the ABP 215 arm vs. ORR in the bevacizumab arm.
	Secondary endpoint	Risk difference of ORR per RECIST v1.1	Risk difference is defined as ORR in the ABP 215 arm minus ORR in the bevacizumab arm.
Database lock	10 September 2015		

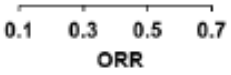
Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent-to-treat population consists of all randomized subjects. All data during study are included in the analyses (Database lock: Sep 10, 2015).		
Descriptive statistics and estimate variability	Treatment group	ABP 215	Bevacizumab
	Number of subject	328	314
	ORR (%)	39.0	41.7
	95% CI (%)*	(33.7, 44.5)	(36.2, 47.4)
Effect estimate per comparison	Risk ratio of ORR	Comparison Group	ABP215 vs. Bevacizumab
		Risk ratio	0.93
		95% CI	(0.77, 1.12)
	Risk difference of ORR	Comparison Group	ABP215 vs. Bevacizumab
		Risk difference (%)	-2.90
		95% CI (%)	(-10.48, 4.67)
Notes			

Analysis performed across trials (pooled analyses and meta-analysis)

In response to CHMP concerns that a loss of efficacy of 11% on the risk difference scale for ORR (95% CI: -10.48% to 4.67% in ITT; 95% CI: -11.06% to 5.42% in PP) is clinically relevant, the applicant provided additional calculations of bevacizumab's ORR based on historical trials from a meta-analysis by Botrel et al 2011 to present the effect of ABP215 in a broader perspective.

Reference	Treatment	N	ORR (95% CI)
Johnson 2004	Bevacizumab + PC	34	0.32 (0.17, 0.51)
Nishio 2009	Bevacizumab + PC	121	0.56 (0.47, 0.65)
Sandler 2006	Bevacizumab + PC	381	0.35 (0.30, 0.40)
Reck 2010	Bevacizumab + GC	329	0.35 (0.30, 0.40)
Study 265	Bevacizumab + PC	314	0.42 (0.36, 0.47)
	ABP 215 + PC	328	0.39 (0.34, 0.45)



ORR and 95% CI calculated based on Botrel TE, et al. *Lung Cancer*. 2011;74:89-97.

Figure 10: ORR results from bevacizumab historical trials in subjects with NSCLC

In order to assess the preservation of treatment effect, the applicant calculated the estimated proportion of bevacizumab's effect retained by ABP 215 (along with a 95% CI). This calculation uses a method that incorporates (or synthesises) the variability of the estimate of bevacizumab's effect relative to placebo and ABP 215's effect relative to bevacizumab. Using this method (Rothmann et al, 2003; Snapinn and Qi, 2008), known as the synthesis method, it is estimated that ABP 215 preserves 83% (95% CI: 44%, 121%) of bevacizumab's effect on the risk difference scale and 89% (95% CI: 57%, 118%) of bevacizumab's effect on the risk ratio scale in the ITT population.

Clinical studies in special populations

N/A

Supportive study(ies)

N/A

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

A single pivotal, randomised, double-blind phase III study (20120265) was conducted in adult subjects with non-squamous NSCLC receiving first-line chemotherapy with carboplatin and paclitaxel to show similarity in efficacy, safety and immunogenicity between the proposed biosimilar ABP 215 and EU reference product Avastin. The patients were randomised 1:1 to receive either ABP 215 or the reference bevacizumab.

The ABP 215 product batches used in the clinical studies can generally be considered representative for commercial production.

All clinical studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and were consistent with International Conference on Harmonisation (ICH) "Guideline for Good Clinical Practice

(GCP)" (ICH E6) as claimed by the applicant. The pivotal phase III efficacy study was conducted in 17 countries of which seven were outside the EU. The Applicant has stated that clinical trials conducted with ABP 215, carried out outside the European Union (EU), meet the ethical requirements of Directive 2001/20/EC, in accordance with Article 6 of Regulation 726/2004 and Article 8 (ib) of Directive 2001/83/EC, as amended.

The chosen patient population of non-squamous NSCLC with the presence of stage IV or recurrent metastatic NSCLC with measurable disease according to modified Recist v1.1, is a homogenous population regarded as a sensitive target population for the purpose of establishing clinical similarity between ABP 215 and reference bevacizumab. Even if maintenance monotherapy with bevacizumab after the active treatment period is indicated in the Avastin SmPC, this was not included in the pivotal phase 3 study, as clearly stated by the Applicant.

Patients with NSCLC expressing activating mutations in EGFRs or ALK translocations were included in the phase 3 study; receptor status assessment was not required at baseline. These patients are known to do less well with up front chemotherapy. Ideally, to reduce unbalanced arms and thereby uncertainty in the data, all patients should have been tested for EGFR and ALK mutations before entering the study; and patients positive for either of the mutation/rearrangement should have been excluded. In addition, to avoid unbalanced enrolment of mutation-negative and mutation-unknown patients, the randomisation of patients harbouring either of these mutations should have been stratified. Therapies targeting the EGF-receptor mutations were approved for first line use in metastatic NSCLC patients already in 2011. However, given that the advice from CHMP in 2011 did not discuss this subject; use of an adequate randomisation procedure when enrolling patients; and in addition, results are indicating similarity between the two products, the chosen strategy is considered acceptable.

The primary endpoint was risk ratio (RR) of best overall response in the ITT population, and the duration of the active treatment (combination regimen) was about 19 weeks.

ORR is considered acceptable as primary endpoint because ORR in NSCLC patients was the most sensitive endpoint observed throughout the original Avastin trials.

The selected primary and secondary outcomes, their measurement time points as well as the pre-selected criteria for biosimilarity are mostly according to the CHMP scientific advice provided, as well as according to relevant CHMP guidelines for biosimilar clinical development.

The inclusion and exclusion criteria used in the phase 3 study are according to the Avastin labelling and therefore considered adequate. The sample size calculations, randomisation and blinding procedures are also considered adequately performed.

According to the Guideline on the choice of the non-inferiority margin (EMEA/CPMP/EWP/2158/99), the CHMP recommends 95% CI in an equivalence setting for proving biosimilarity. The applicant used the 95-95 approach to derive a non-inferiority margin which is acceptable.

The pre-specified equivalence margin for the primary endpoint (RR of ORR) was 0.67 to 1.5. The applicant based the margin on 12.5% for the risk difference in ORR between ABP 2015 and bevacizumab, which is less than the lower bound of 95% CI for the risk difference of ORR derived from a meta-analysis by Botrel et al (2011).

RD of ORR in the PP population was presented in the dossier as one of the secondary end-points. The use of the PP population which is the most sensitive population, in the similarity calculations instead of the ITT population, is considered acceptable.

Patients were sampled for ADAs in approximately one year after randomisation; six months while on active combination treatment with potential suppressive chemotherapy and six months without any treatment.

Efficacy data and additional analyses

RR of ORR was 0.93 (95% CI: 0.77 to 1.12) and RD of ORR was -2.90 (95% CI: -10.48 to 4.67)]. Similarity between ABP 215 and EU-licensed bevacizumab reference product was demonstrated within the pre-specified equivalence margin (0.67, 1.5). The ORR of ABP215 from Study 265 does not deviate considerably from reference bevacizumab results in the previous trials.

In order to more precisely define the primary endpoint and to reduce the masking of differences in the time points of best overall response, it was requested to provide ORR at week 19. The applicant was also requested to present a comparative analysis of response patterns over time showing the proportion of patients with a response at each time point. Results of the risk difference (RD) of ORR from the clinical phase 3 study in NSCLC patients in both the ITT and PP population with 95% CI at week 19, as well as at week seven and 13, confirmed similarity between ABP 125 and reference bevacizumab.

There was a difference in ORR RR between gender and ECOG subgroups which was greater for gender (RR of 1.04 for male, 0.79 for women) than for ECOG subgroups (RR of 1.09 for PS0, 0.83 for PS1). During the procedure, the Applicant provided ORR per treatment arm separately for women and men, and separately for ECOG PS. The proportion of males and females in the ABP215 group achieving ORR was balanced and the difference in RR between genders is driven by the denominator (i.e proportion of women in the bevacizumab arm achieving ORR). It is acknowledged that such deviation in the bevacizumab arm might have arrived by chance, especially given the large number of subgroups studied. It is also noted that although point estimates deviate from 1, the confidence intervals from the subgroups overlap with the confidence interval of the overall effect.

Both the secondary outcomes (PFS, duration of response, tumour burden) and the different sensitivity analyses (investigator assessment) were in line with the primary outcome, supporting the biosimilarity claim between ABP 215 and reference product bevacizumab shown by RR of ORR in the ITT population (primary analysis) and also by RD of ORR in the PP population.

ABP 215 is convincingly demonstrated to be a biosimilar to the bevacizumab reference product is through efficacy comparability studies. The Applicant is claiming the same indications for ABP 215 as granted for the originator Avastin. Since the mechanisms of action are the same, inhibition of tumour vessel growth is expected to be similar across all currently approved cancer indications, extrapolation to all other currently approved indications labelled for the reference product bevacizumab is considered acceptable.

2.4.4. Conclusions on the clinical efficacy

Similarity between ABP 215 and EU-licensed bevacizumab reference product was demonstrated in the ITT and PP population, with RR of ORR within the pre-specified equivalence margin (0.67, 1.5). Equivalence between ABP 215 and reference bevacizumab was also shown by RD of ORR in the ITT and PP population.

Extrapolation to all other indications labelled for the reference product bevacizumab is considered acceptable, given the relevance of the same mechanism of action across indications.

2.5. Clinical safety

Patient exposure

A total of 835 subjects received at least one dose of ABP 215 or bevacizumab (US or EU) IV either as healthy subjects in the phase 1, single-dose clinical pharmacokinetic (PK) study (Study 20110216) or in the phase 3 active-controlled, randomized, double-blind, study of ABP 215 compared with bevacizumab in subjects with advanced NSCLC (Study 20120265). These subjects comprise the safety population.

Pharmacokinetic Similarity Studies in Healthy Subjects - Study 20110216

A phase 1, single-dose clinical pharmacokinetic (PK) study in healthy subjects. Exposure to investigational product was comparable across the treatment groups; 68 received ABP 215, 67 received bevacizumab (US), and 67 received bevacizumab (EU).

Phase 3 Controlled Clinical Study - Study 20120265

An active-controlled, randomized, double-blind, phase 3 study of ABP 215 compared with bevacizumab in subjects with advanced non-squamous non-small cell lung cancer (NSCLC). The median number of doses administered in both the ABP 215 and bevacizumab treatment groups were six.

The end of treatment was at week 19 [+7 days] and it should be noted that no adverse events was recorded during the follow-up phase (after week 19 [+7 days]) except serious adverse events (SAEs) ongoing at the time of the end-of-study visit which will be followed until they resolve or are considered chronic or stable.

The majority of subjects (191 [59.0%] for ABP 215 and 202 [65.4%] for bevacizumab) received 6 doses; 1 subject in the ABP 215 group received 7 doses. The mean (standard deviation [SD]) cumulative total dose of investigational product was 71.3 (26.32) mg/kg for ABP 215 and 74.8 (24.22) mg/kg for bevacizumab.

For paclitaxel and carboplatin subjects were to receive at least 4 cycles of each treatment and no more than 6 cycles with median number of doses administered in both groups being 5.

From the data provided, exposure to the IP and non-IP appears generally comparable across the treatment groups.

Table 22: Investigational Product exposure Summary by Treatment (Study 20120265) (Safety Analysis Population)

Variable	ABP 215 (N = 324)	Bevacizumab (N = 309)
Number of subjects receiving at least 1 dose of IP (n)	324	309
Total number of doses administered		
n	324	309
Mean (SD)	4.8 (1.76)	5.0 (1.61)
Median	6.0	6.0
Min, max	1, 7	1, 6
Cumulative total dose[a] (mg/kg)		
n	320	309
Mean (SD)	71.3 (26.32)	74.8 (24.22)
Median	90.0	90.0
Min, max	15, 105	15, 90
Total number of doses administered (n [%])		
1	25 (7.7)	20 (6.5)
2	37 (11.4)	19 (6.1)
3	15 (4.6)	20 (6.5)
4	33 (10.2)	30 (9.7)
5	22 (6.8)	18 (5.8)
6	191 (59.0)	202 (65.4)
7	1 (0.3)	0 (0.0)

Max = maximum; min = minimum; Q1 = 25th percentile; Q3 = 75th percentile; STD = standard deviation.
Note: A dose delay occurred when the investigational product (IP) Administration eCRF indicated that the dose was given but a reason for dose delay was present. A dose was considered withheld when the IP Administration eCRF indicated that no dose was given and a reason for dose delay was present.
[a]Subjects could have more than one incidence of event. Their corresponding events are displayed for each reason but are only counted once for each reason.

- Disposition of the Study population

Study 20110216

One hundred ninety-one subjects overall (94.6%) completed the study; 11 (5.4%) subjects discontinued the study early. The reason for discontinuation for the majority of these subjects was either withdrawal by the subject (4 subjects, 2.0%) or lost to follow-up (3 subjects, 1.5%).

Study 20120265

59.3% (192 subjects) and 65.4% (202 subjects), respectively, completed treatment. The most common reasons for discontinuing investigational product across both treatment groups were adverse events (77 [12.2%] subjects) and disease progression (78 [12.3%] subjects); the incidence was similar between

groups. Investigational product was discontinued as a result of death for 4.0% (13) subjects in the ABP 215 group and 3.6% (11) subjects in the bevacizumab group.

The percentage of subjects who completed the study was similar between treatment groups (85.2% for ABP 215 and 88.3% for bevacizumab). However, it should be noted that considerably fewer patients in the ABP 215 group (13.6%) plan to receive commercial bevacizumab as compared to the reference group 21.7%).

Adverse events

Study 20110216

In this phase 1 study where a single-dose of ABP 215 or bevacizumab was given, 47.0% of subjects overall reported at least 1 treatment-emergent adverse events (TEAEs). The majority of these events were assessed as grade 1 or 2 (mild to moderate). There were no deaths, SEAs, or TEAEs leading to discontinuation of the study.

No major safety concerns or signals were identified in this single dose study. However, of notice, more TEAEs were reported in the ABP 215 and bevacizumab (EU) treatment groups (EU sourced bevacizumab carried out at EU site) compared with the ABP 215 and bevacizumab (US) treatment group (US sourced bevacizumab carried out at US site). In relation to this and in order to better understand these site differences the Applicant did a post hoc analysis of the TEAEs by study site. This analysis shows that the frequency, type and severity of TEAEs were similar within each site: In the US site TEAEs was reported in 37.1% (13 subjects) in the ABP 215 group and 32.8% (22 subjects) in the bevacizumab (US) group; the subject incidence for the EU site was 57.6% (19 subjects) for ABP 215 and 61.2% (41 subjects) for bevacizumab (EU). It was concluded that the differences in adverse event rates between sites are likely due to types of adverse events reported in different geographic locations in an otherwise healthy population.

Table 23: Treatment-emergent Adverse Events Reported in ≥5% of Subjects in Any Treatment Group by Preferred Term (Study 20110216) (Safety Population)

Preferred Term	ABP 215 (N = 68) n (%)	Bevacizumab (US) (N = 67) n (%)	Bevacizumab (EU) (N = 67) n (%)	Overall (N = 202) n (%)
Subjects with any TEAE	32 (47.1)	22 (32.8)	41 (61.2)	95 (47.0)
Headache	6 (8.8)	10 (14.9)	16 (23.9)	32 (15.8)
Nasopharyngitis	4 (5.9)	0	11 (16.4)	15 (7.4)
Nausea	2 (2.9)	4 (6.0)	1 (1.5)	7 (3.5)
Pharyngitis	0	0	5 (7.5)	5 (2.5)
Vessel puncture site hematoma	4 (5.9)	0	1 (1.5)	5 (2.5)

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Note: TEAEs were defined as all events starting or worsening after commencement of treatment with investigational product. Adverse events were coded using MedDRA, Version 15.0.

Study 20120265

Overall, the majority of subjects (597 subjects; 94.3%) reported at least 1 TEAE (Table 24). In the ABP 215 group, the subject incidence was 95.1% (308 subjects, 2,643 events) and in the bevacizumab group the subject incidence was 93.5% (289 subjects, 2,712 events). For approximately half of these subjects (276 subjects, 43.6% overall), the severity of at least one TEAEs was grade 3 or higher.

Table 24: Overall Summary of Treatment-emergent Adverse Events (Study 20120265) (Safety Analysis Population).

Category	ABP 215 (N = 324) n (%)	Bevacizumab (N = 309) n (%)	Total (N = 633) n (%)
Any TEAE	308 (95.1)	289 (93.5)	597 (94.3)
Any grade ≥ 3 TEAE	139 (42.9)	137 (44.3)	276 (43.6)
Any fatal TEAE	13 (4.0)	11 (3.6)	24 (3.8)
Any serious TEAE	85 (26.2)	71 (23.0)	156 (24.6)
TEAE leading to discontinuation of IP	61 (18.8)	53 (17.2)	114 (18.0)
TEAE leading to discontinuation of any component of chemotherapy	68 (21.0)	52 (16.8)	120 (19.0)

IP = investigational product; TEAE = treatment-emergent adverse event.
Note: Only TEAEs are summarized. For each category, subjects are included only once, even if they experienced multiple events in that category.

The TEAEs reported by 5% or more of subjects in either the ABP 215 or bevacizumab treatment group are summarized in Table 25. The most frequently reported TEAEs were alopecia, nausea, and anemia.

For three TEAEs a 5% difference between the two treatment groups were observed: nausea (25.6% in the ABP 215 group and 30.7% in the bevacizumab group), diarrhoea (13.0% and 18.1%, respectively), and peripheral neuropathy (17.3% and 12.3%, respectively).

Table 25: Treatment-emergent Adverse Events Experienced by ≥ 5% of Subjects in Either Treatment Group by Preferred Term (Study 20120265) (Safety Analysis Population).

	ABP 215 (N = 324)		Bevacizumab (N = 309)	
Preferred Term	Number of Subjects n (%)	Number of Events	Number of Subjects n (%)	Number of Events
Any adverse event [a]	308 (95.1)	2643	289 (93.5)	2712
Alopecia	140 (43.2)	167	127 (41.1)	159
Nausea	83 (25.6)	126	95 (30.7)	163
Anaemia	67 (20.7)	115	64 (20.7)	98
Neutropenia	60 (18.5)	119	61 (19.7)	115
Fatigue	59 (18.2)	72	59 (19.1)	84
Neuropathy peripheral	56 (17.3)	86	38 (12.3)	60
Decreased appetite	54 (16.7)	65	43 (13.9)	53
Hypertension	51 (15.7)	66	41 (13.3)	70
Asthenia	49 (15.1)	91	42 (13.6)	62
Thrombocytopenia	49 (15.1)	86	43 (13.9)	81
Epistaxis	45 (13.9)	50	39 (12.6)	60
Diarrhoea	42 (13.0)	54	56 (18.1)	81
Myalgia	39 (12.0)	78	44 (14.2)	76
Vomiting	38 (11.7)	46	42 (13.6)	55
Constipation	37 (11.4)	40	36 (11.7)	48
Paraesthesia	29 (9.0)	35	40 (12.9)	50
Headache	28 (8.6)	30	24 (7.8)	32
Dyspnoea	27 (8.3)	29	26 (8.4)	32
Proteinuria	26 (8.0)	39	19 (6.1)	25
Cough	26 (8.0)	30	21 (6.8)	21
Pain in extremity	24 (7.4)	28	20 (6.5)	20
Leukopenia	23 (7.1)	38	23 (7.4)	56
Arthralgia	23 (7.1)	25	30 (9.7)	49
Polyneuropathy	20 (6.2)	26	22 (7.1)	28
Bone pain	20 (6.2)	24	25 (8.1)	33
Pyrexia	20 (6.2)	23	21 (6.8)	29
Peripheral sensory neuropathy	18 (5.6)	23	16 (5.2)	34
Weight decreased	18 (5.6)	19	16 (5.2)	16
Stomatitis	15 (4.6)	17	18 (5.8)	26
Back pain	14 (4.3)	15	20 (6.5)	23
Dizziness	13 (4.0)	17	25 (8.1)	33
Gingival bleeding	9 (2.8)	9	19 (6.1)	22

Note: Adverse events are coded using MedDRA version 18.0. Only treatment-emergent adverse events are summarized. For each preferred term, a subject is included only once, even if they had multiple events in that preferred term. Multiple events are counted separately in the Number of Events column.

[a] Includes all subjects experiencing any treatment-emergent adverse event, regardless of incidence.

The overall safety profile as reflected by the most frequently reported TEAEs and the severity of the TEAEs including by causality, appears generally comparable in both treatment arms.

Adverse events of interest (EOI)

Study 20120216

EOI were not analysed.

Study 20120265

The prespecified EOIs were derived based on the MOA and clinical data available in prescribing information for the reference product (Avastin).

The incidence of any EOI in the ABP 215 and bevacizumab treatment were 76.2% and 74.1%, respectively. The most frequently reported EOIs grade ≥ 3 were neutropenia and infections (16.7% for ABP 215 and 15.2% for bevacizumab), infusion reaction (9.6% and 6.8%, respectively), and hypertension (6.8% and 5.5%, respectively).

- Infusion Reaction Adverse Events

In both groups, hypertension (ABP 215: 15.7%, bevacizumab: 13.3%) and myalgia (12.0% and 14.2%, respectively) were reported most frequently. Events that were grade 4 in the ABP 215 were respiratory failure in 2 subjects and respiratory distress in 1 subject; in the bevacizumab group, the grade 4 event was hypertension and the grade 5 event was sudden death.

Table 26: Infusion Reaction Treatment-emergent Adverse Events (EOI Narrow Search) in ≥1% of Subjects in Either Treatment Group by Preferred Term (Study 20120265) (Safety Analysis Population)

Category	ABP 215 (N = 324) n (%)	Bevacizumab (N = 309) n (%)	Total (N = 633) n (%)
Any infusion reaction TEAE	133 (41.0)	125 (40.5)	258 (40.8)
Hypertension	51 (15.7)	41 (13.3)	92 (14.5)
Myalgia	39 (12.0)	44 (14.2)	83 (13.1)
Pyrexia	20 (6.2)	21 (6.8)	41 (6.5)
Blood pressure increased	9 (2.8)	8 (2.6)	17 (2.7)
Hypotension	8 (2.5)	6 (1.9)	14 (2.2)
Rash	8 (2.5)	13 (4.2)	21 (3.3)
Syncope	5 (1.5)	6 (1.9)	11 (1.7)
Hypersensitivity	4 (1.2)	2 (0.6)	6 (0.9)

EOI = event of interest; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Note: Adverse events are coded using MedDRA version 18.0. Only TEAEs are summarized. For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term.

- Peripheral Sensory Neuropathy Adverse Events

A 5 % higher incidence is observed for the ABP215 arm as compared to the bevacizumab arm for peripheral sensory neuropathy adverse events. The events for 6 (1.9%) subjects in the ABP 215 group and 5 (1.6%)

subjects in the bevacizumab group were grade 3. The majority of peripheral neuropathy TEAEs were grade 1 and 2.

Table 27: Peripheral Sensory Neuropathy Treatment-emergent Adverse Events (SMQ Narrow Search) in ≥ 1% of Subjects in Either Treatment Group by Preferred Term (Study 20120265) (Safety Analysis Population).

Category	ABP 215 (N = 324) n (%)	Bevacizumab (N = 309) n (%)	Total (N = 633) n (%)
Any peripheral sensory neuropathy TEAE	97 (29.9)	78 (25.2)	175 (27.6)
Neuropathy peripheral	56 (17.3)	38 (12.3)	94 (14.8)
Polyneuropathy	20 (6.2)	22 (7.1)	42 (6.6)
Peripheral sensory neuropathy	18 (5.6)	16 (5.2)	34 (5.4)

MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standard MedDRA query; TEAE = treatment emergent adverse event.
Note: Adverse events are coded using MedDRA version 18.0. Only TEAEs are summarized. For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term.

- Neutropenia and Infection Adverse Events

In both groups, events of neutropenia (18.5% [60 subjects] for ABP 215 and 19.7% [61 subjects] for bevacizumab) and leukopenia (7.1% [23 subjects] and 7.4% [23 subjects], respectively) were reported most frequently. In the ABP 215 and bevacizumab groups, events for 4.9% (16 subjects) and 3.9% (12 subjects), respectively, were serious.

Table 28: Neutropenia and Infection Treatment-emergent Adverse Events (SMQ Narrow Search) in ≥ 1% of Subjects in Either Treatment Group by Preferred Term (Study 20120265) (Safety Analysis Population)

Category	ABP 215 (N = 324) n (%)	Bevacizumab (N = 309) n (%)	Total (N = 633) n (%)
Any neutropenia and infection TEAE	84 (25.9)	80 (25.9)	164 (25.9)
Neutropenia	60 (18.5)	61 (19.7)	121 (19.1)
Leukopenia	23 (7.1)	23 (7.4)	46 (7.3)
Febrile neutropenia	13 (4.0)	8 (2.6)	21 (3.3)
Neutrophil count decreased	5 (1.5)	5 (1.6)	10 (1.6)
White blood cell count decreased	2 (0.6)	5 (1.6)	7 (1.1)
Lymphopenia	0 (0.0)	3 (1.0)	3 (0.5)

MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standard MedDRA query; TEAE = treatment emergent adverse event.
Note: Adverse events are coded using MedDRA version 18.0. Only TEAEs are summarized. For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term.

- Thrombotic Microangiopathy Adverse Events

The 2 most common thrombotic microangiopathy events were thrombocytopenia (49 [15.1%] subjects for ABP 215 and 43 [13.9%] subjects for bevacizumab) and proteinuria (26 [8.0%] and 19 [6.1%] subjects, respectively). The events for 2 subjects in the ABP 215 group were fatal.

Table 29: Thrombotic Microangiopathy Treatment-emergent Adverse Events (EOI Narrow Search) in ≥ 1% of Subjects in Either Treatment Group by Preferred Term (Study 20120265) (Safety Analysis Population)

Category	ABP 215 (N = 324) n (%)	Bevacizumab (N = 309) n (%)	Total (N = 633) n (%)
Any thrombotic microangiopathy TEAE	76 (23.5)	59 (19.1)	135 (21.3)
Thrombocytopenia	49 (15.1)	43 (13.9)	92 (14.5)
Proteinuria	26 (8.0)	19 (6.1)	45 (7.1)

EOI = event of interest; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: Adverse events are coded using MedDRA version 18.0. Only TEAEs are summarized. For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term.

Haemorrhage Adverse Events

Haemorrhage events were serious for 3.4% of ABP 215 subjects and 2.3% of bevacizumab subjects. The outcome related to haemorrhage was fatal for 5 patients (haemoptysis (2 subjects [0.6 %]), rectal haemorrhage (2 subjects [0.6 %]) and gastrointestinal haemorrhage (1 subject [0.3 %])) in the ABP 215 group and 2 patients (haemoptysis (2 subjects [0.6 %]) in the bevacizumab group.

Table 30: Haemorrhage Treatment-emergent Adverse Events (SMQ Narrow Search) in ≥ 1% of Subjects by Preferred Term (Study 20120265) (Safety Analysis Population)

Category	ABP 215 (N = 324) n (%)	Bevacizumab (N = 309) n (%)	Total (N = 633) n (%)
Any hemorrhage TEAE	72 (22.2)	66 (21.4)	138 (21.8)
Epistaxis	45 (13.9)	39 (12.6)	84 (13.3)
Haemoptysis	14 (4.3)	8 (2.6)	22 (3.5)
Gingival bleeding	9 (2.8)	19 (6.1)	28 (4.4)

MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standard MedDRA query; TEAE = treatment emergent adverse event.
Note: Adverse events are coded using MedDRA version 18.0. Only TEAEs are summarized. For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term.

- Pulmonary Haemorrhage Adverse Events

4.3% (14 subjects) in the ABP 215 treatment group and 3.2% (10 subjects) in the bevacizumab treatment group were identified with pulmonary haemorrhage TEAEs; these events were reported as “haemoptysis” for all subjects but 2, which were reported as “pulmonary haemorrhage” (bevacizumab treatment group). Across all the pulmonary haemorrhage TEAEs, the events for 3 subjects in the ABP 215 group and 6 subjects in the bevacizumab group were serious. By grade, across the treatment groups, events were grade 5 for 2 subjects receiving ABP 215; and 2 subjects receiving bevacizumab.

- Reversible Posterior Leukoencephalopathy Syndrome (PRES) Adverse Events

Sixteen subjects (4.9%) in the ABP 215 treatment group and 9 subjects (2.9%) in the bevacizumab treatment group were identified as having TEAEs possibly related to reversible posterior leukoencephalopathy syndrome. Two events were reported in ≥ 1% of subjects in either the ABP 215 or bevacizumab treatment group (Table 31). Events were grade 3 and 4 for one subject each in the ABP 215 group and grade 4 and 5

for 1 subject each in the bevacizumab group. None of the events were associated with a clinical context that was suggestive of PRES.

Table 31: Reversible Posterior Leukoencephalopathy Syndrome-related Treatment-emergent Adverse Events (EOI Narrow Search) in ≥ 1% of Subjects in Either Treatment Group by Preferred Term (Study 20120265) (Safety Analysis Population)

Category	ABP 215 (N = 324) n (%)	Bevacizumab (N = 309) n (%)	Total (N = 633) n (%)
Any reversible posterior leukoencephalopathy syndrome-related TEAE	16 (4.9)	9 (2.9)	25 (3.9)
Visual impairment	4 (1.2)	0 (0.0)	4 (0.6)
Vision blurred	3 (0.9)	4 (1.3)	7 (1.1)

EOI = event of interest; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Note: Adverse events are coded using MedDRA version 18.0. Only TEAEs are summarized. For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term.

- Arterial Thromboembolic Adverse Events

The standard search identified 1.9% (6 subjects) in the ABP 215 treatment group and 1.3% (4 subjects) in the bevacizumab treatment group with arterial thromboembolic TEAEs; all events occurred in <1% of subjects in either group. Also, all of the arterial thromboembolic TEAEs were serious in both treatment groups, and the events were fatal (grade 5) for 2 subjects in the ABP 215 treatment group.

- Gastrointestinal perforation adverse events

The standard search identified 0.9% (3 subjects) in the ABP 215 group and 1.3% (4 subjects) in the bevacizumab group with GI perforation TEAEs. Across all of the GI perforation TEAEs, the events were serious for 2 subjects in the ABP 215 group (grade 5 for 1 subject) and serious for all 4 subjects in the bevacizumab group (none were grade 5).

- Congestive heart failure adverse events

Two subjects in the ABP 215 treatment group and 1 subject in the bevacizumab with one or more congestive heart failure TEAEs were identified. For 1 subject in each group, the events were serious and grade 5.

- Non-gastrointestinal fistula formation adverse events

Two subjects in the ABP 215 treatment group and 2 subjects in the bevacizumab treatment group were identified with one or more non-GI fistula formation TEAEs. For 1 subject in the ABP 215 group, the event was serious and grade 4; for 1 subject in the bevacizumab group, the event was serious and grade 5.

Serious adverse event / deaths / other significant events

Deaths

Study 20110216.

There were no deaths during the study.

Study 20120265.

There were 24 deaths in total. The fatal events that occurred in more than one subject in either treatment group were death (2 subjects [0.6%] in the ABP 215 group [verbatim terms were “death NOS” for 1 subject and “death (unknown)” for the other] versus 1 subject [0.3%] in the bevacizumab group [verbatim term “death of unknown reason”), hemoptysis (2 subjects [0.6 %] in both the ABP 215 group and the bevacizumab group), and rectal haemorrhage (2 subjects [0.6 %] in the ABP 215 group). All other events occurred in 1 subject in a single treatment group.

On review of the individual case narratives in the CSR:

- 4 fatal TEAEs were reported as related to the IP - 2 in the ABP 215 group (Intestinal perforation and Rectal Haemorrhage) and 2 in the bevacizumab group (Haemoptysis and Bronchial fistula).
- 2 fatal TEAEs were reported as related to the IP, paclitaxel and carboplatin – 2 in the ABP 215 group (Rectal haemorrhage and Ischaemic cerebral infarction).
- 1 fatal TEAE was reported as related to paclitaxel and carboplatin in the ABP 215 treatment group (thrombocytopenia).
- The remaining 17 fatal TEAEs were reported as not related to the IP, paclitaxel or carboplatin.

The incidence of any fatal TEAE due to disease progression was 4 (1.2%) subjects in the ABP 215 treatment group (events of cardiac arrest, cardiopulmonary failure, death, and haemoptysis) and 2 (0.6%) subjects in the bevacizumab treatment group (events of brain oedema and general health deterioration).

Table 32: Fatal Treatment-emergent Adverse Events by Preferred Term (Study 20120265) (Safety Analysis Population)

Category	ABP 215 (N = 324) n (%)	Bevacizumab (N = 309) n (%)	Total (N = 633) n (%)
Any fatal TEAE	13 (4.0)	11 (3.6)	24 (3.8)
Death[a]	2 (0.6)	1 (0.3)	3 (0.5)
Haemoptysis	2 (0.6)	2 (0.6)	4 (0.6)
Rectal haemorrhage	2 (0.6)	0 (0.0)	2 (0.3)
Cardiac arrest	1 (0.3)	0 (0.0)	1 (0.2)
Cardiopulmonary failure	1 (0.3)	0 (0.0)	1 (0.2)
Gastrointestinal haemorrhage	1 (0.3)	0 (0.0)	1 (0.2)
Intestinal perforation	1 (0.3)	0 (0.0)	1 (0.2)
Ischaemic cerebral infarction	1 (0.3)	0 (0.0)	1 (0.2)
Mesenteric artery embolism	1 (0.3)	0 (0.0)	1 (0.2)
Thrombocytopenia	1 (0.3)	0 (0.0)	1 (0.2)
Acute left ventricular failure	0 (0.0)	1 (0.3)	1 (0.2)
Brain oedema	0 (0.0)	1 (0.3)	1 (0.2)
Bronchial fistula	0 (0.0)	1 (0.3)	1 (0.2)
General physical health deterioration	0 (0.0)	1 (0.3)	1 (0.2)
Hypercoagulation	0 (0.0)	1 (0.3)	1 (0.2)
Pneumonia	0 (0.0)	1 (0.3)	1 (0.2)
Sepsis	0 (0.0)	1 (0.3)	1 (0.2)
Sudden death	0 (0.0)	1 (0.3)	1 (0.2)

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Note: Adverse events are coded using MedDRA version 18.0. Only TEAEs are summarized. For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term.
a Cause of death was not provided for these subjects.

Serious adverse events (SAE)

Study 20110216.

No serious adverse events were reported.

Study 20120265.

One or more serious adverse event were reported in 85 (26.2%) subjects in the ABP 215 treatment group and 71 (23.0%) subjects in the bevacizumab treatment group. The serious adverse event reported most frequently was febrile neutropenia: 11 subjects (3.4%) and 8 subjects (2.6%) in the ABP 215 group and bevacizumab group, respectively. An overview of SAEs observed in ≥ 1 % are given in the table below.

Table 33: Serious Treatment-emergent Adverse Events Experienced by ≥ 1 % of Subjects in Either Treatment Group by Preferred Term (Study 20120265) (Safety Analysis Population).

Preferred Term	ABP 215 (N = 324) n (%)	Bevacizumab (N = 309) n (%)
Subjects with any SAE	85 (26.2)	71 (23.0)
Febrile neutropenia	11 (3.4)	8 (2.6)
Neutropenia	6 (1.9)	3 (1.0)
Pneumonia	6 (1.9)	5 (1.6)
Pulmonary embolism	5 (1.5)	6 (1.9)
Anaemia	3 (0.9)	6 (1.9)
Dyspnoea	3 (0.9)	4 (1.3)
Haemoptysis	3 (0.9)	5 (1.6)

MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Note: Adverse events are coded using MedDRA version 18.0. Only TEAEs are summarized. For each system organ class and preferred term, a subject is included only once, even if they experienced multiple events in that system organ class or preferred term.

Overall survival was a safety endpoint in this study. Results from the analysis showed no clinically meaningful differences between the ABP 215 and bevacizumab treatment groups: 43 (13.3%) subjects and 36 (11.7%) subjects, respectively, died during treatment or during the follow-up period.

Laboratory findings

Study 20110216

Overall, the profile of laboratory abnormalities was similar across treatment groups. However, three healthy volunteers experienced TEAEs of abnormal LFTs, all subjects were in the ABP 215 arm. Abnormal LFTs are not a listed ADR for bevacizumab and no signal was identified in the clinical efficacy/safety study in patients with NSCLC.

For two cases, it seems likely the results were exercise induced and these asymptomatic cases resolved before the end of the study without medical intervention. For the last subject, the event had not resolved at the time the subject withdrew from the study, he was found to have a positive Hepatitis A IgG result but IgM was negative. Abnormal LFTs are not a listed ADR for bevacizumab and no signal was identified in the much larger clinical efficacy/safety study in patients with NSCLC who received multiple higher doses of bevacizumab compared with the single dose in the healthy volunteer study. The cause of these results in this single subject remains unclear and the subject was lost to follow-up.

Study 20120265

All clinically significant (grade ≥ 3) subjects with postbaseline haematology and serum chemistry results are summarized in **Error! Reference source not found.**. Overall, the results obtained for clinical laboratory parameters were similar between the ABP 215 and bevacizumab groups. There were no major concerns in safety signals from the laboratory investigations.

- Haematology laboratory results

White (leukocytes and neutrophils) and red (haemoglobin and haematocrit) blood cell parameters and platelets all decreased approximately 10% to 25% over the course of treatment. The decreases were similar in both the ABP 215 and bevacizumab group except for the decrease in median platelet, which was greater in the ABP 215 group than in the bevacizumab group.

The majority of subject incidences listed in **Error! Reference source not found.** were grade 3 events. Two (0.6%) subjects in both ABP 215 and bevacizumab had grade 4 decreases in leukocytes. Eleven (3.4%) and 5 subjects (1.6%) on ABP 215 and bevacizumab, respectively, had grade 4 decreases in neutrophils. One (0.3%) and 5 subjects (1.6%) on ABP 215 and bevacizumab, respectively, had grade 4 platelet decreases.

Table 34: Subject Incidence of Grade ≥ 3 Postbaseline Hematology and Serum Chemistry Results (Safety Analysis Population)

Lab Parameter	ABP 215 (N=324) n (%)	Bevacizumab (N=309) n (%)	Total (N=633) n (%)
Hematology			
Leukocytes	12 (3.7)	5 (1.6)	17 (2.7)
Neutrophils	25 (7.7)	12 (3.9)	37 (5.8)
Hemoglobin - Decrease	7 (2.2)	12 (3.9)	19 (3.0)
Hemoglobin - Increase	0 (0.0)	1 (0.3)	1 (0.2)
Platelets	9 (2.8)	17 (5.5)	26 (4.1)
Serum Chemistry			
Alanine Aminotransferase	1 (0.3)	1 (0.3)	2 (0.3)
Aspartate Aminotransferase	2 (0.6)	1 (0.3)	3 (0.5)
Bilirubin	1 (0.3)	0 (0.0)	1 (0.2)
Alkaline Phosphatase	3 (0.9)	2 (0.6)	5 (0.8)
Sodium – Decrease	15 (4.6)	13 (4.2)	28 (4.4)
Sodium – Increase	0 (0.0)	1 (0.3)	1 (0.2)
Potassium – Decrease	2 (0.6)	1 (0.3)	3 (0.5)
Potassium – Increase	2 (0.6)	4 (1.3)	6 (0.9)
Albumin	3 (0.9)	1 (0.3)	4 (0.6)
Glucose – Decrease	1 (0.3)	1 (0.3)	2 (0.3)
Glucose – Increase	10 (3.1)	11 (3.6)	21 (3.3)
Creatinine	2 (0.6)	0 (0.0)	2 (0.3)

Note: For each laboratory parameter, subjects are counted only once even if the subject has multiple grade ≥ 3 postbaseline results for that parameter. CTCAE grading for glucose - decrease and glucose - increase for this study is based on non-fasting glucose.

Safety in special populations

specific studies assessing the potential impact of safety in special groups of ABP 215, have not been conducted.

Immunological events

All samples from the PK similarity study in healthy subjects (Study 20110216) were screened for binding ADAs using a validated 2-tiered immunoassay approach (screening assay and specificity assay; see assessment of the assays under Pharmacokinetics and Methods above). Only two samples were collected from each patient, at baseline and at day 85, end-of study. Evaluations of immunogenicity were also conducted in the phase 3 safety and efficacy study (20120265), using the same methodology as that used in the PK similarity study. All binding ADA-positive samples were to be assessed for neutralising antibodies using a target binding assay.

In the phase 3 study (20120265), patients were sampled for ADAs in the end of each treatment cycle, together with pharmacokinetic sampling; baseline, week 7, week 13 and week 19.

Two validated assays, subject to resolution of outstanding issues, were used to detect the presence of anti-ABP 215 antibodies. All available protocol-specified samples were first tested in an electro-chemiluminescence (ECL)-based bridging immunoassay to detect antibodies capable of binding to ABP 215 (Binding Antibody Assay). Samples confirmed to be positive for binding antibodies were subsequently tested in a non-cell based target binding assay to determine neutralising activity against ABP 215 (Neutralising Antibody Assay). If a post-dose sample was positive for binding antibodies and demonstrated neutralising activity at the same time point, the sample was defined as positive for neutralising antibodies.

- Anti-drug Antibodies

In the pivotal PK study, a total of 199 subjects were tested for anti-ABP 215 antibodies. There were no pre-existing ADAs detected in baseline blood samples for either treatment group, and no subjects tested positive for binding ADAs after end-of study. No differences in anti-ABP 215 antibody rates were observed across groups treated with ABP 215, Bevacizumab (US), or Bevacizumab (EU). If present in the sample, drug concentration in all tested antibody samples was below the levels which may interfere with the detection of anti-ABP 215 binding antibodies in the immunoassay.

In the safety and efficacy study, the overall incidence of developing binding ADAs at week 19, after end-of combination treatment, first phase of the study, was 1.9% (1.4% [4 subjects] for ABP 215 and 2.5% [7 subjects] for bevacizumab); i.e. four out of 294 (1.4%) evaluable subjects in the ABP 215 arm and 7 out of 284 (2.5%) evaluable subjects in the bevacizumab arm developed binding ADAs on study. Three subjects (1% and 1.1%) in each arm developed transient ADAs, meaning the results on ADAs were negative at the subject's last time point tested within the study period. No subject in either treatment arm tested positive for neutralising antibodies. Results from isolated samples were presented to support the assertion that the risk of false negative tests for ADA was low; further assays of the end of study (EOS) samples for ADA were performed to mitigate the risk of false negatives. EOS sera were tested for ADA by standard protocol from 95 of 102 subjects, (ABP 215 = 49, bevacizumab = 46). One (subject 26551001019, bevacizumab group) of 95 subjects tested was positive for binding ADA and negative for neutralizing ADA after EOT.

Table 35: Anti-drug Antibody Results (Safety Analysis Population)

Variable	ABP 215 (N = 324)	Bevacizumab (N = 309)	Total (N = 633)
Subjects with an on-study result (N1)[a]	320	307	627
Total antibody incidence [n (%)][b]			
Binding antibody positive anytime	4 (1.3)	10 (3.3)	14 (2.2)
Neutralizing antibody positive anytime	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with a result at baseline (N2)	315	303	618
Pre-existing antibody incidence [n (%)][c]			
Binding antibody positive at baseline	0 (0.0)	3 (1.0)	3 (0.5)
Neutralizing antibody positive at baseline	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with a result at any postbaseline visit (N3)	294	284	578
Developing antibody incidence [n (%)][d]			
Binding antibody positive postbaseline with a negative or no result at baseline	4 (1.4)	7 (2.5)	11 (1.9)
Transient[e]	3 (1.0)	3 (1.1)	6 (1.0)
Neutralizing antibody positive postbaseline with a negative or no result at baseline	0 (0.0)	0 (0.0)	0 (0.0)
Transient[e]	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with a postbaseline result by Week 7	286	279	565
Developing antibody incidence (n)			
Binding antibody positive with a negative or no result at baseline	2	2	4
Neutralizing antibody positive with a negative or no result at baseline	0	0	0
Subjects with a postbaseline result by Week 13	294	283	577
Developing antibody incidence (n)			
Binding antibody positive with a negative or no result at baseline	3	3	6
Neutralizing antibody positive with a negative or no result at baseline	0	0	0
Subjects with a postbaseline result by Week 19	294	284	578
Developing antibody incidence (n)			
Binding antibody positive with a negative or no result at baseline	4	6	10
Neutralizing antibody positive with a negative or no result at baseline	0	0	0

Note: Baseline is defined as the last non-missing assessment taken prior to the first dose of study therapy. Visit values are windowed using the upper bound of study analysis visits centered on the nominal visit day.
[a]Subjects considered on-study after signing informed consent.
[b]Percentages are calculated as n/N1* 100.
[c]Percentages are calculated as n/N2* 100.
[d]Percentages are calculated as n/N3* 100.
[e]Negative result at the subject's last time point tested within the study period.

Safety related to drug-drug interactions and other interactions

No drug-drug interactions studies were submitted.

Discontinuation due to adverse events

Study 20120265

A higher number of patients discontinued carboplatin and/or paclitaxel because of adverse events on ABP 215 compared to bevacizumab [74 (22.8%) vs 59 subjects (19.1%), respectively]. The types and frequencies of adverse events leading to chemotherapy dose reductions were similar on ABP 215 and bevacizumab.

Table 36: Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Product in ≥ 1% of Subjects in Either Treatment Group by Preferred Term (Safety Analysis Population)

Preferred Term	ABP 215 (N = 324) n (%)	Bevacizumab (N = 309) n (%)
Subjects with any TEAE leading to discontinuation of IP	61 (18.8)	53 (17.2)
Pulmonary embolism	5 (1.5)	6 (1.9)
Haemoptysis	4 (1.2)	5 (1.6)
Neuropathy peripheral	4 (1.2)	0 (0.0)
Thrombocytopenia	4 (1.2)	0 (0.0)
Pneumonia	3 (0.9)	3 (1.0)
Asthenia	2 (0.6)	3 (1.0)
Dyspnoea	2 (0.6)	3 (1.0)
Fatigue	2 (0.6)	3 (1.0)

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event
Note: Adverse events are coded using MedDRA version 18.0. Only TEAEs are summarized. For each preferred term, a subject is included only once, even if they experienced multiple events in that preferred term.

Post marketing experience

N/A

2.5.1. Discussion on clinical safety

A total of 835 subjects were treated with one or more doses of ABP 215 or bevacizumab in two clinical studies; a single-dose phase 1 study (study 20110216) in healthy male subjects and an active-controlled, randomized, double-blind, phase 3 study (study 20120265) of ABP 215 compared with bevacizumab in subjects with advanced non-squamous NSCLC. The number of subjects is considered sufficient to study safety signals in this comparability exercise.

In the phase 1 study a single dose of 3-mg/kg intravenous (IV) was administered and 15 mg/kg every 3 weeks (Q3W) for 6 treatment cycles was administered in the phase 3 study. Thus, fewer TEAEs are expected in the single dose phase 1 study as compared to the phase 3 study.

In the phase 1 study more TEAEs were reported in the ABP 215 (57.6%) and bevacizumab (EU) (61.2%) treatment groups (EU sourced bevacizumab carried out at EU site) compared with the ABP 215 (37.1%) and bevacizumab (US) (32.8%) treatment group (US sourced bevacizumab carried out at US site). However, the frequency, type and severity of TEAEs were similar within each site supporting biosimilarity. In the pivotal phase 3 study the end of treatment was defined at week 19 [+7 days] and it should be noted that adverse events were not monitored during the follow-up phase (after end-of-treatment; week 19 [+7 days]), except SAEs ongoing at the time of the end-of-study visit which will be followed until they resolve or are considered chronic or stable. An end of treatment at week 19 [+7 days], after 6 cycles of combination therapy, is considered to be on the short side in order investigate and register safety signals.Most of the safety signals for bevacizumab have been recorded during the combination phase (in the early cycles) and hence the monitoring period should be sufficient to uncover safety signals. However, it should be stressed that patients are immunosuppressed when on chemotherapy. Thus, continuation with monotherapy would have been preferable in this study as this could potentially have uncovered chemotherapy suppressed immunogenicity signals (and related safety events).

In both the ABP 215 and bevacizumab treatment groups of the phase 3 study, exposure to investigational product, paclitaxel, and carboplatin was generally similar, but a higher number of subjects receiving two doses in the ABP 215 as compared to the bevacizumab group for all treatments (37 subjects vs 19 subjects for the investigational product exposure, 39 subjects vs 20 subjects for the paclitaxel exposure and 37 subjects vs 19 subjects for the carboplatin exposure, respectively) were reported. In total, discontinuation of investigational product due to a TEAE was similar between the two groups with (18.8% in the ABP 215 treatment group compared to 17.2% in the bevacizumab treatment group). Of notice, a slightly higher number of patients discontinued carboplatin and/or paclitaxel because of adverse events (21.0% and 16.8% in the ABP 215 and bevacizumab group, respectively). These slight differences between the two treatment groups are considered not to have any clinical impact.

In general, the number, type, and severity of TEAEs in the two groups of the pivotal study phase 3 are similar and in line with the safety profile for bevacizumab. Importantly, no new safety signals or safety patterns were reported for ABP 215. Also, the incidence of subjects experiencing any AE were similar in the two groups (95.1% in the ABP 215 group, and 93.5% in the bevacizumab group). For approximately half of these subjects (42.9% in the ABP 215 group, and 44.3% in the bevacizumab group), the severity of at least one TEAE was grade 3 or higher. The largest differences (≥5%) between the two groups were detected for nausea (25.6% in the ABP 215 group and 30.7% in the bevacizumab group) and diarrhoea (13.0% in the ABP 215 group and 18.1%, in the bevacizumab group), but as no events were serious this is considered acceptable.

There were 24 deaths, 13 (4.0 %) in the ABP 215 treatment group and 11 (3.6 %) in the bevacizumab treatment group in the phase 3 study. Most of these were events that occurred in one single patient with no pattern revealed, hence they are considered acceptable given the well-known safety profile of the reference product. The fatal events that occurred in more than one subject in a single treatment groups by preferred term were related to bleeding (5 subjects in the ABP 215 arm versus 2 in the bevacizumab arm). Overall, these numbers are considered acceptable with no new AE patterns revealed. Also, on review of the individual case narratives: 4 fatal TEAEs were reported as related to the IP, 2 in each treatment group; 2 fatal TEAEs were reported as related to the IP, paclitaxel and carboplatin, both in the ABP 215 group; and 1 fatal TEAE

was reported as related to paclitaxel and carboplatin in the ABP 215 group. The remaining 17 fatal TEAEs were reported as not related to the IP, paclitaxel or carboplatin. The incidence of any fatal TEAE due to disease progression was 4 (1.2%) subjects in the ABP 215 treatment group and 2 (0.6%) subjects in the bevacizumab treatment group.

The number of patients that developed ADAs was low in the phase 3 study; 7 and 4 patients in the bevacizumab and ABP215 groups, respectively. Overall, the results obtained for clinical laboratory parameters were similar between the ABP 215 and bevacizumab groups with no major concerns in safety signals. The variations between the ABP 215 and the bevacizumab group on the haematology parameters, in particular the difference in neutrophils (25 [7.7%] and 12 subjects [3.9%] on ABP 215 and bevacizumab, respectively) are noteworthy. Still, no difference between the two groups was reported for the TEAE of neutropenia (18.5% [60 subjects] for ABP 215 and 19.7% [61 subjects] for bevacizumab), leukopenia (7.1% [23 subjects] and 7.4% [23 subjects], respectively). For febrile neutropenia the differences are considered minor (4% [13 subjects] for ABP 215 and 2.6% [8 subjects] for bevacizumab). Based on this, these differences in neutrophils are considered not to be of concern. The median platelet values for subjects in the ABP 215 and bevacizumab group were similar at baseline, and by week 19 median decreases from baseline were greater in the ABP 215 group (-109.50 x 10^9/L) than in the bevacizumab group (-76.00 x 10^9/L). However, these differences are not considered to be of clinical concern.

2.5.2. Conclusions on the clinical safety

The number and type of TEAEs were comparable between ABP 215 and bevacizumab, and from a safety and immunogenicity point of view biosimilarity between ABP 215 and the reference product Avastin has been shown.

The clinical safety information under sections 4.4, 4.5 and 4.8 of the Avastin SmPC applies also to Mvasi.

2.6. Risk Management Plan

Safety concerns

Table 37: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Bleeding/haemorrhage • Pulmonary haemorrhage • Proteinuria • Arterial thromboembolic events • Hypertension • Congestive heart failure • Wound healing complications • Gastrointestinal perforations

	• Reversible posterior leukoencephalopathy syndrome • Neutropenia • Venous thromboembolic events • Fistula (other than gastrointestinal) • Thrombotic microangiopathy • Pulmonary hypertension • Ovarian failure • Hypersensitivity reactions/infusion reactions • Gall bladder perforation • Peripheral sensory neuropathy • Cardiac disorders (excluding congestive heart failure and arterial thromboembolic events) • Osteonecrosis of the jaw • Necrotizing fasciitis • Adverse events following off-label intravitreal use • Embryo-fetal development disturbance • Osteonecrosis in children
Important potential risks	• Not applicable
Missing information	• Safety profile of the different treatment combinations in patients with non-squamous non-small cell lung cancer • Long-term effects of MVASI when used in the paediatric population • Safety and efficacy in patients with renal impairment • Safety and efficacy in patients with hepatic impairment • Use in lactating women

Pharmacovigilance plan

Routine pharmacovigilance activities are considered sufficient to identify and/or further characterise the above safety concerns and to assess the effectiveness of the risk minimisation measures. This is in accordance with the reference product.

The ongoing paediatric studies for the reference medicinal product are not considered relevant for the biosimilar.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Bleeding/ Hemorrhage	Wording in sections 4.4 and 4.8 of the SmPC	None
Pulmonary haemorrhage	Wording in sections 4.4 and 4.8 of the SmPC	None
Proteinuria	Wording in sections 4.4, 4.5 and 4.8 of the SmPC	None
Arterial thromboembolic events	Wording in sections 4.4 and 4.8 of the SmPC	None
Hypertension	Wording in sections 4.4, 4.5, 4.8 and 5.1 of the SmPC	None
Congestive heart failure	Wording in sections 4.4 and 4.8 of the SmPC	None
Wound healing complications	Wording in sections 4.4, 4.8 and 5.3 of the SmPC	None
Gastrointestinal perforations	Wording in sections 4.4 and 4.8 of the SmPC	None
Reversible posterior leukoencephalopathy syndrome	Wording in sections 4.4, 4.5 and 4.8 of the SmPC	None
Neutropenia	Wording in sections 4.4, 4.5 and 4.8 of the SmPC	None
Venous thromboembolic events	Wording in sections 4.4 and 4.8 of the SmPC	None
Fistula (other than gastrointestinal)	Wording in sections 4.4 and 4.8 of the SmPC	None
Thrombotic microangiopathy	Wording in section 4.8 of the SmPC	None
Pulmonary hypertension	Wording in section 4.8 of the SmPC	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Ovarian failure	Wording in sections 4.4, 4.6 and 4.8 of the SmPC	None
Hypersensitivity reactions/infusion reactions	Wording in sections 4.3, 4.4 and 4.8 of the SmPC	None
Gall bladder perforation	Wording in sections 4.4 and 4.8 of the SmPC	None
Peripheral sensory neuropathy	Wording in section 4.8 of the SmPC	None
Cardiac disorders (excluding congestive heart failure and arterial thromboembolic events)	Wording in section 4.8 of the SmPC	None
Osteonecrosis of the jaw	Wording in sections 4.4 and 4.8 of the SmPC	None
Necrotizing fasciitis	Wording in sections 4.4 and 4.8 of the SmPC	None
Adverse events following off-label intravitreal use	Wording in section 4.4 of the SmPC	None
Embryo-foetal development disturbance	Wording in sections 4.6, 4.8 and 5.3 of the SmPC	None
Osteonecrosis in children	Wording in section 4.8 of the SmPC	None
Safety profile of the different treatment combinations in patients with non-squamous non-small cell lung cancer	Wording in sections 4.4 and 4.8 of the SmPC	None
Long-term effects of MVASI when used in the paediatric population	Wording in sections 4.2 and 4.8 of the SmPC	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Safety and efficacy in patients with renal impairment	Wording in sections 4.2, 4.8 and 5.2 of the SmPC	None
Safety and efficacy in patients with hepatic impairment	Wording in sections 4.2 and 5.2 of the SmPC	None
Use in lactating women	Wording in section 4.6 of the SmPC	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.3 is acceptable.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.8. Product information

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

The package leaflet of Mvasi has the same content as that of the reference medicinal product Avastin.

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, MVASI (bevacizumab) is included in the additional monitoring list as it is a biological product authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this

medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Mvasi has been developed as a biosimilar of bevacizumab using Avastin as a reference medicinal product. The indications applied for are treatment of patients with metastatic carcinoma of the colon or rectum; metastatic breast cancer; metastatic non-squamous non-small cell lung cancer (NSCLC); metastatic renal cell carcinoma; metastatic cervical cancer; and epithelial ovarian, fallopian tube, or primary peritoneal cancer.

3.1.2. Main clinical studies

A PK study was performed in healthy subjects and the primary objective was to demonstrate bioequivalence of ABP 215 relative to EU-sourced, as well as US-sourced Avastin (bevacizumab) following a 3 mg/ kg body weight single i.v. injection.

A phase 3 study for the efficacy and safety comparison of ABP 215 with the reference product bevacizumab, including monitoring of immunogenicity, was submitted by the Applicant. This was a randomised, double-blind, active-controlled study in adult subjects with non-squamous NSCLC receiving first-line chemotherapy with carboplatin and paclitaxel in addition to ABP 215 and bevacizumab, respectively, for 6 cycles. The primary endpoint was risk ratio (RR) of ORR in the ITT population and secondary endpoints were RD of ORR, duration of response and PFS.

3.2. Favourable effects

The purpose of this application is to demonstrate similarity of ABP 215 to the reference product bevacizumab. Thus, there is no requirement to demonstrate benefit to the patient per se as this has been shown for the reference product. The biosimilarity approach has been assessed from a quality, non-clinical, pharmacokinetic and clinical perspective, and the conclusion is based upon the totality of the submitted data.

From a quality and non-clinical perspective, data has been presented supporting that ABP 215 can be considered a biosimilar to the bevacizumab reference product.

From a pharmacokinetic perspective, bioequivalence has been demonstrated between ABP 215 and bevacizumab (Avastin). The primary endpoints (i.e. AUC_{last}, AUC_{inf} and C_{max}) with their 90% confidence intervals are well within the predefined acceptance range of 80-125%.

The geometric LS means ratios for the comparison of ABP 215 and EU sourced Avastin for AUC_{last}, AUC_{inf} and C_{max} were 1.03, 0.96 and 0.96 and the corresponding 90%CIs [0.982-1.080], [0.916-1.006], [0.920-1.004], respectively.

From a pharmacokinetic perspective, ABP 215 can be considered similar to the bevacizumab reference product.

- **From a Clinical perspective**

A phase 3 study in advanced NSCLC has been performed aiming at showing similarity in efficacy, safety and immunogenicity between the proposed biosimilar ABP 215 and EU-licensed Avastin. The primary efficacy endpoint was the risk ratio (RR) of objective response rate (ORR) in the ITT population, according to RECIST version 1.1, as assessed by the central, independent, blinded radiologist. 95% CI for RR and risk difference (RD) of ORR in the ITT population [ABP 215/bevacizumab, RR of ORR was 0.93 (95% CI: 0.77 to 1.12); RD of ORR was -2.90 (95% CI: -10.48 to 4.67)] were within the pre-specified equivalence margin (0.67, 1.5 and 12.5%) and indicated similarity between ABP 215 and bevacizumab reference product).

Similarity was also shown by RR and RD of ORR in the per protocol (PP) population (secondary analysis of the primary endpoint), within the predefined boundaries for equivalence of 0.67 to 1.5 for RR based on 12.5% for the risk difference [RR of ORR: 0.94 (95% CI: 0.78 to1.13) and RD of ORR: -2.82% (95% CI: -11.06% to 5.42%)].

The results of the secondary efficacy endpoints were also similar between the two treatment arms (ITT population: DOR medians of 5.8 for ABP 215 (95% CI: 4.9 to 7.7 months) and 5.6 months for bevacizumab (95% CI: 5.1 to 6.3 months); PFS medians were 6.6 for ABP 215 (95% CI: 6.3 to 7.9 months) and 7.9 months for bevacizumab (95% CI: 6.6 to 8.2 months).

Several sensitivity analyses (e.g. based on investigator's assessment or other patient populations) also support similarity between ABP 215 and the reference product bevacizumab.

3.3. Uncertainties and limitations about favourable effects

No uncertainties remain on the favourable effects.

3.4. Unfavourable effects

Overall, the safety profile for the biosimilar ABP 215 is comparable to the reference product Avastin during the treatment period of 19 weeks [+7 days] with combination therapy, both in terms of TEAE, SAEs, deaths, discontinuation of treatment due to AEs and laboratory findings.

The ADA-positive rates after 19 weeks (end-of-treatment) were zero for ABP 215 and the reference bevacizumab in the pivotal PK study, and low for both in the safety and efficacy study (4 and 6 patients with ADAs at week 19 in the ABP 215 group and Avastin group, respectively).

3.5. Uncertainties and limitations about unfavourable effects

The phase 3 efficacy and safety study was not continued with monotherapy of ABP 215 or bevacizumab after the six cycles with combination therapy, and safety signals are thereby not available for the final phase of the study (follow-up). As patients are immunosuppressed when on chemotherapy, this may supress the production of ADAs, and also related adverse events. Thus, preferably, patients should have continued on monotherapy in the follow-up phase until end-of study as they are more prone to develop ADAs in a state when they only receive investigational products (bevacizumab) and chemotherapy has been ended.

However based on the totality of the safety data submitted, there are no new safety signals, hence the safety profile of ABP 215 is considered adequate.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The totality of results collected from the quality, non-clinical data, pharmacokinetics and clinical studies supports similarity between ABP 215 and the reference product bevacizumab.

3.6.2. Balance of benefits and risks

Since the similarity of ABP 215 to the bevacizumab reference product was convincingly demonstrated through comparability studies both at the quality, non-clinical and clinical level the benefit – risk for Mvasi follows the benefit-risk balance for the reference product bevacizumab (Avastin) and is positive.

3.6.3. Additional considerations on the benefit-risk balance

3.7. Conclusions

The overall B/R of MVASI is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Mvasi is not similar to Lynparza, Torisel, Yondelis and Zejula within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Mvasi is favourable in the following indications:

MVASI in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum.

MVASI in combination with paclitaxel is indicated for first-line treatment of adult patients with metastatic breast cancer. For further information as to human epidermal growth factor receptor 2 (HER2) status, please refer to section 5.1.

MVASI, in addition to platinum-based chemotherapy, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology.

MVASI, in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations (see section 5.1).

MVASI in combination with interferon alfa-2a is indicated for first-line treatment of adult patients with advanced and/or metastatic renal cell cancer.

MVASI, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of adult patients with advanced (International Federation of Gynecology and Obstetrics (FIGO) stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer (See section 5.1).

MVASI, in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents.

MVASI in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin is indicated for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents (see section 5.1).

MVASI, in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the

RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

EXHIBITS 4-11

THESE DOCUMENTS

HAVE BEEN REDACTED

IN THEIR ENTIRETY

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GENENTECH, INC. and CITY OF HOPE,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	
	)	
AMGEN INC.	)	C.A. No. 17-1407-CFC
	)	(Consolidated)
Defendant.	)	
	)	
	)	
	)	
	)	

[PROPOSED] ORDER GRANTING PLAINTIFFS' DISCOVERY REQUESTS

IT IS HEREBY ORDERED, this _____ day of _____, 2019, that:

1. Paragraph 28 of the Stipulated Protective Order in this case (D.I. 209) is modified to read as follows:

"CONFIDENTIAL Discovery Material produced by a Party or Third Party may be used by a Receiving Party only for purposes of this Litigation or future United States patent infringement litigation between the Parties arising from Defendant's filing of Biologics License Application No. 761028 or litigation initiated by the filing of the Complaint provided by Genentech to Amgen on January 28, 2019."

2. Within seven (7) days of this Order, Defendant shall produce all materials responsive to Plaintiffs' Requests for the Production of Documents and Things Nos. 111-113 and 123; shall produce unredacted copies of Exhibits __ and __ to Plaintiffs' March 8, 2019 letter; and shall remove redactions for "Ex-US" information from other previously produced documents.

3. Within seven (7) days of this Order, Defendant shall produce all materials responsive to Plaintiffs' Request for the Production of Documents and Things Nos. 118, and shall provide a complete answer to Plaintiffs' Interrogatory No. 14.
4. Within seven (7) days of this Order, Defendant shall produce all materials responsive to Plaintiffs' Requests for the Production of Documents and Things No. 128; shall produce unredacted copies of Exhibits __ and __ to Plaintiffs' March 8, 2019 letter; and shall remove redactions for information regarding Defendants' process for manufacturing other products from other previously produced documents.
5. Within seven (7) days of this Order, Defendant shall produce all materials responsive to Plaintiffs' Requests for the Production of Documents and Things No. 133 that relate to measurements of dissolved oxygen levels.
6. Within seven (7) days of this Order, Defendant shall produce all materials responsive to Plaintiffs' Requests for the Production of Documents and Things Nos. 129-131.

_____

UNITED STATES DISTRICT JUDGE

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GENENTECH, INC. and CITY OF HOPE,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	
	)	
AMGEN INC.	)	C.A. No. 17-1407-CFC
	)	(Consolidated)
Defendant.	)	
	)	
	)	
	)	
	)	

AVERMENT OF COUNSEL

I, Daniel M. Silver, hereby aver that a reasonable effort was made to resolve the disputes addressed in the foregoing letter, and that such efforts included oral communication that involved Delaware counsel.

Dated: March 8, 2019

Respectfully Submitted,

/s/ Daniel M. Silver
Daniel M. Silver (# 4758)

CERTIFICATE OF SERVICE

The undersigned counsel hereby certifies that true and correct copies of the foregoing document were caused to be served on March 8, 2019 on the following counsel in the manner indicated:

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Dated: March 8, 2019

/s/ Daniel M. Silver
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